Evaluation of correlations of Plasma Levels of Oxytocin, Omentin-1 and Irisin in Diabetic and Non-Diabetic Metabolic Syndrome Patients: A Cross Sectional Study in Jordan

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Abstract

Metabolic syndrome (Mets) risk factor biomarkers, namely oxytocin (OXT), omentin-1 and irisin, plasma levels were evaluated via colorimetric enzymatic bioassays. A total of 195 Mets patients were recruited from the outpatients' diabetes and endocrinology clinics at the National Center for Diabetes Endocrinology and Genetics. Participants were subdivided according to their fasting glycemia status into either the normoglycemic subjects group (Mets-controls) or dysglycemic subjects group (Mets-pre/T2DM). Enrolled recruits in both study arms were BMI (body mass index)-, gender- and age-matched.

Distinctively in the Mets-pre/T2DM group; mean circulating levels of both OXT (pg/mL) and omentin-1 (ng/mL) were significantly lower but mean irisin plasma levels (ng/mL) were substantially higher ($p<0.01$ vs. respective Mets-controls'). Markedly, in the total pool of Mets-participants, plasma OXT levels correlated inversely with irisin plasma levels but proportionally with omentin-1 plasma levels; [Spearman correlation coefficient $r = -0.377$(N=147) for irisin and $r = 0.321$(N=138) for omentin-1]. Meanwhile, omentin-1 plasma levels correlated inversely ($p<0.001$) with irisin's [$r = -0.309$(N=121)]. These findings indicate that like OXT, irisin and omentin-1 can be postulated as surrogate biomarkers and/or putative pharmacologic agents to limit the deleterious effect of chronic subclinical inflammatory process among Mets individuals with glucose profile abnormalities compared to apparently healthy Mets ones.

Keywords: Oxytocin, Metabolic Syndrome, Omentin-1, Irisin; Type 2 Diabetes Mellitus, Jordan.

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Introduction

Diabetes mellitus (DM) is a complex, multi-factorial, chronic metabolic and endocrine disorder. It is characterized by the presence of hyperglycemia that can be caused by defects in insulin secretion, insulin action, or both[(1)]. Most of cases of diabetes fall into two broad

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categories: type 1 and type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is due to a progressive insulin secretory defect on the background of insulin resistance (IR)[1]. Obesity plays an important role in the development of chronic low-grade inflammation. The state of chronic low-grade inflammation associated with excess adipose tissue explains the development of the obesity-related pathologies. It plays an important role in the development of IR that triggers the associated comorbidities of Mets, such as atherosclerosis, dyslipidemia, hypertension, and hyperglycemia[2,3]. Obesity-induced IR along with impaired insulin secretion from pancreatic beta cells contribute towards the development of T2DM[4].

Oxytocin (OXT) is a neurohypophysial hormone produced by hypothalamic OXT neurons. The systemic action of OXT mediates the reproductive activities of females including laboring and lactation[5]. OXT was found to be involved in several functions other than labor and lactation. The chronic central infusion of OXT, dose-dependently restricted weight gain and increased adipose tissue lipolysis in rats with high fat diet (HFD)-induced obesity[6]. In addition to regulating body weight balance, OXT also improves lipid profile, promotes glucose uptake, stimulates insulin secretion and reverses IR[7, 8,4]. Thus, OXT is closely tied with a marked pharmacologic value as a new class of anti-diabetic polypeptide agents very similar to the glucagon-like peptide (GLP-1) to treat diabetes[4].

A considerable attention was given to the myokine, irisin, as a potential therapeutic agent for treating obesity and diabetes. Irisin is released into the blood where it drives brown-fat-like conversion of white adipose tissues (WAT)[9]. The conversion of white adipocytes to brown adipocytes and the resultant increase in thermogenesis leads to improved glucose tolerance, increased insulin sensitivity, lower body weight, and decreased fat mass[10,11]. Unexpected high levels of irisin have been observed in obese animals and humans[12,13]. The adipokine,omentin-1, is also considered to be a promising therapeutic target for treating diabetes since it proved to have insulin-sensitizing actions[14]. Its expression is found to be reduced in obesity, IR and T2DM[15]. The lower plasma omentin-1 levels actually contribute to the pathogenesis of IR and T2DM in obese patients[15].

The novelty of our clinical study is being the first of its kind conducted to evaluate the link between Mets biomarkers (omentin-1 and irisin) and plasma OXT levels in the metabolic syndrome-diabetic patients. In case of establishing the relationship between OXT levels and obesity-diabetes biomarkers dysregulation (omentin-1 and irisin), it would be possible to provide a therapeutic suggestion about the neuropeptide OXT intervention as an anti-obesity and anti-diabetic agent.

Methods

The association between OXT and Mets biomarkers[16] (omentin-1 and irisin) was evaluated in 195 Mets patients (64 Mets males and 131 Mets females) who visited the outpatient endocrinology and diabetes clinics of NCDEG, all of them were completely naïve to anti-hyperglycemic medications and they were either overweight (>25 kg/m^2) or obese (>30 kg/m^2). Patients were subdivided to 92 apparently healthy Mets participants and were assigned as Mets-control group and 103 pre-diabetics or newly diagnosed with T2DM and were assigned as Mets-pre/T2DM, each experimental arm was subdivided into males and females as illustrated in Figure 1. The response rate was 95%.

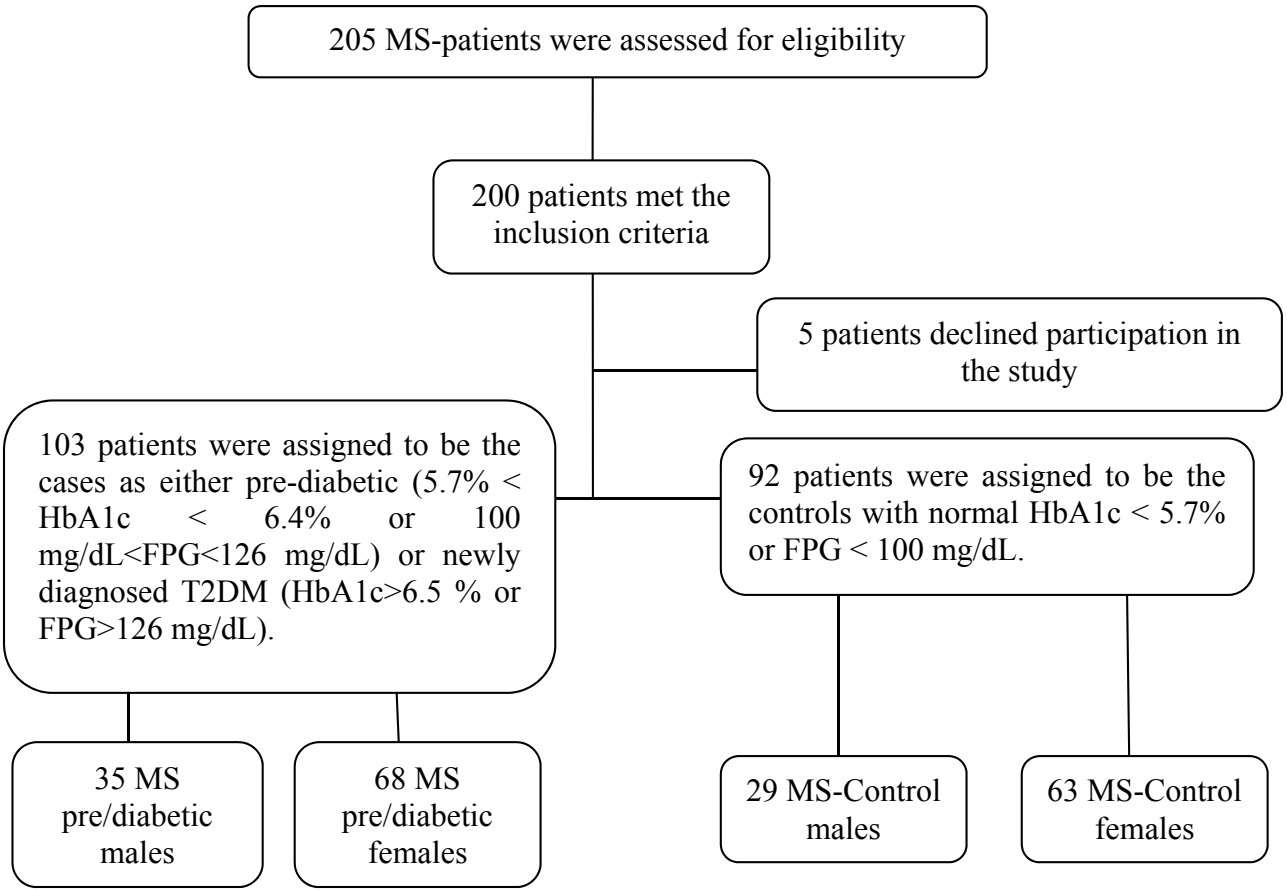

Figure 1. The study flowchart

Clinical settings and duration

The study was conducted in the period between August and December 2014 .After obtaining a signed informed consent and approval from the scientific research committee at the School of Pharmacy, The University of Jordan, Institutional Review Board (IRB) committee at the National Center for Diabetes Endocrinology and Genetics (NCDEG) (MS/9/5211) and Jordan University Hospital (L/18/2014). Exclusion criteria were 1) pregnant or lactating women, 2) patients who had any prior treatment with anti-diabetic agents, 3) patients with clinical evidence of autoimmune or life threating disease (alcohol/drug abuse/dyslipdimia/recently diagnosed with untreated endocrine disorder), 4) Individuals with inflammatory disease such as the inflammatory bowel disease, or 5) subjects with obesity secondary to an endocrine dearrangement.

The demographic data (weight, height, waist circumeference and blood pressure) were measured in co-operation with the nursing team. Blood was collected from each participant for biochemcal analyses (HbA1c, Fasting Plasma Glucose (FPG), Fasting Lipid Profile (FLP) and other biomarkers) and performed in the clinical laboratories of NCDEG and JUH. In addition, patients' medical history of delivery of overweight neonates (>4

kg), polycystic ovarian syndrome (PCOS) in women, as well as history of coronary artery diseases (CAD) and DM in first degree relatives. Lifestyle data such as smoking and physical activity were collected from patients themselves. BMI was calculated by using the following equation: BMI=weight(kg)/ height $(m)^2$.[16]

Laboratory assay work principles

Plasma samples were subjected to refrigerated centifugation technique on fresh withdawn blood samples at 2000 round per minute (RPM) for 10 minutes at 4 C^o . then, the plasma aliguotes were kept at -80 C^o till the time of biochemical analysis.

Statistics

All biomarkers tests were carried out with 2 independent experiments, all data were tested for normality of distribution. All results are expressed as mean ±SD. Pre-coded data were entered into statistical package for the social science software release 20 (SPSS® Inc., Chicago, IL), Categorical data were expressed as frequency and percentage; while continuous variables were presented as mean ± SD. Independent sample t-test was utilized to compare continuous data among two categories. Chi-square test was utilized as appropriate to compare two sets of categorical data. Correlations between biomarkers and clinical parameters were assessed using Spearman correlation due to non-normal data distribution. All probabilities were two tailed and p-value < 0.05 was regarded as statistically significant.

Results

Patients' demographic data

The majority of participants (67.2%) were females. The mean age was 51.26±10.45 years and the mean BMI was 33.32±5.47 kg/m^2. There were no statistically significant variations in the demographic characteristics such as age, gender, or BMI between the Mets-control and Mets-pre/T2DM groups (p>0.05) which demonstrates the homogeneity of the study pool of participants (Table 1).

Table 2 displays the lack of gender dimorphism in metabolic risk biomarkers plasma levels in undiabetic Mets-control participants.

Table 1. Demographic characteristics of the study Mets-participants

Parameter	Total sample, N=195	METS-Control group, N=92	METS-Pre/T2DM group, N=103	p^b value
Age in years, mean ± SD	51.26±10.45	50.49±9.84	51.95±10.97	0.332
Gender, N (%)[a*] Male Female	 64 (32.8) 131 (67.2)	 29 (31.5) 63 (68.5)	 35 (34.0) 68 (66.0)	0.715*
BMI (mean ± SD) (kg/m^2)	33.32±5.47	33.12±4.97	33.51±5.93	0.633

[p]Percent within total. [b]p-value by independent-sample t-test for age, and BMI. *By Chi-square test for gender. BMI: body mass index.

Table 2. Lack of gender dimorphism in metabolic risk biomarkers plasma levels in undiabetic Mets-control participants

Metabolic risk biomarker	MetS-control		
	Males, N=29 (mean±SD)	Females, N=63 (mean±SD)	p^b value
OXT (pg/mL)	1928.83±936.02	2224.08±940.55	0.185
Omentin-1 (ng/mL)	4.35±4.32	5.81±5.84	0.315
Irisin (ng/mL)	122.36±29.26	135.53±30.33	0.086

[b]*p*-value by independent-sample t-test

Table 3. Clinical characteristics of Mets participants and comparison between both study groups

Clinical parameter	METS-total sample			METS-control			METS-pre/T2DM		
	METS-Males, N=64 (mean±SD)	METS-Females, N=131 (mean±SD)	p^b value	Males, N=29 (mean±SD)	Females, N=63 (mean±SD)	p^b value	Males, N=35 (mean±SD)	Females, N= 68 (mean±SD)	p^b value
SBP (mm Hg)	138.54±17.07	135.55±18.85	0.293	137.48±14.61	131.03±18.53	0.102	139.50±19.21	139.74±18.30	0.953
DBP (mm Hg)	82.31±10.36	79.82±11.50	0.151	80.90±7.84	77.61±10.89	0.149	83.59±12.20	81.82±11.76	0.489
Waist circumference (cm)	**108.30±12.40**	**103.28±12.04**	**0.008**	**107.69±8.53**	**101.33±11.79**	**0.011**	108.82±15.05	105.09±12.06	0.178
Serum creatinine (mg/dL)	**0.85±0.22**	**0.65±0.1702**	**<0.001**	**0.81±0.23**	**0.61±0.14**	**<0.001**	**0.88±0.21**	**0.68±0.19**	**<0.001**
HbA_1c (%)	7.06±9.55	5.82±0.81	0.145	5.34±0.55	5.35±0.57	0.973	8.49±12.81	6.28±0.74	0.167
FPG (mg/dL)	113.90±27.96	109.12±24.53	0.235	105.00±22.08	99.50±14.78	0.175	121.24±30.38	117.97±28.23	0.598
Total cholesterol (mg/dL)	197.40±42.62	199.24±43.98	0.805	202.17±40.68	194.22±47.29	0.490	193.33±44.56	203.41±40.96	0.306
LDL-C (mg/dL)	135.60±36.82	129.88±38.14	0.335	133.59±42.26	123.34±36.78	0.246	137.48±31.51	135.64±38.65	0.817
HDL-C (mg/dL)	**39.93±11.40**	**50.59±21.61**	**0.001**	**40.07±7.70**	**54.52±28.02**	**0.009**	**39.80±14.15**	**46.84±11.94**	**0.014**
TG (mg/dL)	166.23±104.63	157.34±83.19	0.532	173.66±122.16	140.90±62.72	0.101	159.29±86.60	171.37±95.55	0.550
OXT (pg/mL)	1442.52±857.14	1637.64±920.37	0.167	1928.83±936.02	2224.08±940.55	0.185	1067.37±561.65	1141.43±531.97	0.516
Omentin-1 (ng/mL)	3.38±3.50	4.54±6.33	0.260	4.35±4.32	5.81±5.84	0.315	2.54±2.37	3.48±6.58	0.508
Irisin (ng/mL)	740.87±685.91	732.54±651.56	0.941	122.36±29.26	135.53±30.33	0.086	1235.68±537.84	1222.93±485.67	0.911

[a]*p*-value by independent-sample t-test. FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin (A_1c), HDL-C: high density lipoprotein, LDL-C: low density lipoprotein, TG: triglycerides. BP: blood pressure.

Differences in clinical characteristics and biomarker levels in both study arms

The clinical characteristics and parameters levels of the study population are summarized in Table 3. The following parameters were significantly higher in the Mets-pre/T2DM group compared to the Mets-control group: systolic BP (139.66±18.50 vs. 133.07±17.57 mm Hg; p=0.012); diastolic BP (82.39±11.87 vs. 78.66±10.09 mmHg; p=0.021); creatinine (0.75±0.21 vs. 0.67±0.20 mg/dL; p=0.019); HbA1c (7.05±7.61 vs. 5.35±0.56; p=0.034); and FPG (119.11±28.89 vs. 101.29±17.56 mg/dL; p<0.001). Omentin-1 was significantly

higher in the Mets-control group than in the Mets-pre/T2DM group, while irisin was substantially higher in the Mets-pre/T2DM group than in the Mets-control group. The mean omentin-1 plasma levels in the Mets-control group and Mets-pre/T2DM group were 5.39±5.45 ng/mL and 3.22±5.72 ng/mL, respectively (p=0.019) and mean irisin plasma levels were 131.01±30.41 ng/mL and 1227.38±501.35 ng/mL, respectively, (p<0.001). Like omentin-1, mean OXT plasma levels were lower in the Mets-pre/T2DM group than in the Mets-control group, 1115.51±540.87 pg/mL vs. 2126.87±943.65 pg/mL, respectively (p<0.001).

Correlations between OXT, omentin-1 and irisin levels and between these biomarkers and clinical parameters

The correlation of clinical parameters with biomarkers in total pool of Mets-participants, Mets-control group, and Mets-pre T2DM group are summarized in Table 4. Plasma OXT levels correlated inversely with irisin but directly with omentin-1 levels in the total pool of Mets-participants (p<0.001, r=-0.377 and p<0.001, r=0.321 respectively). OXT also correlated inversely with HbA1c (p<0.001, r=-0.351), fasting plasma glucose (FPG) (p=0.012, r=-0.193), and creatinine (p=0.033, r=-0.165) in the total pool of Mets-participants, but correlated directly with LDL-C (p=0.004, r=0.294) in the Mets-pre/T2DM group. Interestingly, omentin-1 in the total population of the Mets-study correlated negatively with irisin (p=0.001, r=-0.309) and with all of the HbA1c (p=0.004, r=-0.234), SBP (p=0.011, r=-0.209), and DBP (p=0.01, r=-0.212). However, omentin-1 showed a positive correlation with total cholesterol (TC) in both the total pool of Mets-participants and Mets-pre/T2DM group (p=0.021, r=0.210 and p=0.031,r=0.260 respectively). It also correlated positively with LDL-C in the Mets-pre/T2DM group (p=0.006, r=0.309), but negatively with DBP in the Mets-control group (p=0.036, r=-0.255). Irisin correlated directly with HbA1c (p<0.001, r=0.603), FPG (p<0.001, r=0.382), and TG (p=0.009, r=0.214) in the total Mets-population. It additionally correlated directly with TG in the Mets-Pre/T2DM group (p=0.007, r=0.298). An inverse correlation was observed between irisin and creatinine in the Mets-pre/T2DM group (p=0.022, r=-0.257) and between irisin and LDL-C in the Mets-control group (p=0.026, r=-0.272).

Discussion

In comparison to the study by Qian et al.[17], on 88 subjects with newly diagnosed T2DM of a total of 176 patients enrolled, OXT finding were comparable to the results of our study mainly in those with NGT obese patients versus T2DM obese patients only (Table 5).

A recent study by Jialal et al.[18] had enrolled a total of 75 subjects, divided into individuals with nascent Mets (without the complications of diabetes or CVD), and into control subjects who had ≤2 features of Mets and were not on any blood pressure medication. Plasma omentin-1 levels (ng/mL) were found to be lower in nascent Mets participants compared to non-METS controls (p=0.004). Furthermore, the study by Greulich *et al*.[19] enrolled a total of 92 subjects subdivided into 78 men with uncomplicated T2DM and 14 healthy men (controls) with normal glucose metabolism. This also showed that circulating omentin-1 levels (ng/mL) were lower in patients with T2DM vs. controls (p=0.008). In agreement with these two studies, Gürsoy *et al*.[20], who conducted a study on Mets females, reported that plasma omentin-1 levels (ng/mL) of the

diabetic patients (307.9 ± 153.1) were significantly lower than in the control participants (461.0 ± 153.2) ($p<0.001$). Similarly, our study plasma omentin-1 levels in the Mets-pre/T2DM female patients (3.48±6.58) were lower than the Mets-control females (5.81±5.84). Gürsoy *et al*.[20] enrolled a total of 120 subjects. These involved 80 newly diagnosed type 2 diabetic female patients and 40 age-matched female control subjects. Unlike our study, in Gürsoy et al.,[20] study, the inverse relationships of BMI- IR and all related glucose and profile intolerance were clearly delineated in diabetic and nondiabetic females only. Our study pool of participants had both genders of prediabetic/diabetic and nondiabetic Mets patients. In Qian et al.,[18] study, significant variations in TG, HDL-C and OXT levels were reported between all participating 4 groups of lean normoglycemic recruits and lean diabetic patients, normoglycemic obese vs. diabetic obese participants. Our study is highly unprecedented due to its comprehensiveness in evaluating these biomarkers in newly diagnosed diabetics and prediabetics who are also drug naïve with Mets components. This experimental design was not ever reported to be implemented in comparing the undiabetic Mets vs. prediabetic and diabetic Mets subjects.

Our irisin findings are in consistency with a recent study[20], where a total of 151 subjects (71 men and 80 women) were recruited. 27.8% of the participants had Mets. Plasma irisin levels were compared between subjects who had Mets and those who were healthy. It was found that circulating irisin concentrations were significantly higher in individuals with Mets versus those without Mets ($p<0.001$). Our results confirm these findings where we also reported that Mets-pre/T2DM group had significantly higher plasma irisin levels (ng/mL) (1227.38±501.35) than Mets-control group (131.01±30.41) ($p<0.001$).

The correlation between relatively decreased levels of OXT and dysregulation of some diabetes-METS biomarkers i.e. (omentin-1 and irisin) have been investigated for the first time in this study. Our goal was to support conducting more interventional trials investigating OXT-omentin1, OXT-irisin and omentin1-irisin causality relationship via providing OXT, omentin-1 or Irisin as new pharmacotherapies in metabolic disturbances like obesity, IR, and diabetes management. Furthermore, we also studied the correlations of metabolic biomarkers with clinical parameters (SBP, DBP, HbA1c, waist circumference, BMI, and lipid profile) in both Mets-control and Mets-pre/T2DM groups. Pronounced discrepancies between the undiabetic Mets vs. prediabetic and diabetic Mets participants were of much clinical relevance mostly in recruiting eligible subjects and subsequent allocation to either study group based to glycemia parameters (HbA_1c (%) and FPG).

Future studies should take into consideration important factors that can have an effect on OXT levels such as acute stress and circadian rhythm. Also, molecular studies concerning the mechanisms underlying correlations between the three biomarkers as well as between the biomarkers and clinical characteristics in Mets patients may suggestively be conducted.

Table 4. Correlations for plasma levels of OXT, omentin-1, irisin and clinical parameters in the total study Mets-population, and in the two study groups

Correlation of Clinical parameter		Total Mets-sample			METS-Control group			METS-Pre/T2DM group		
		OXT	**Omentin-1**	**Irisin**	**OXT**	**Omentin-1**	**Irisin**	**OXT**	**Omentin-1**	**Irisin**
Systolic blood pressure	Correlation	-0.029	**-0.209***	0.068	0.032	-0.193	-0.031	0.149	-0.155	-0.020
	Sig.(2-tailed)	0.697	**0.011**	0.403	0.777	0.113	0.801	0.146	0.172	0.858
	N	179	**148**	155	82	69	70	97	79	85
Diastolic blood pressure	Correlation	-0.031	**-0.212****	0.125	0.044	**-0.255***	-0.076	0.137	-0.097	-0.005
	Sig.(2-tailed)	0.683	**0.010**	0.124	0.699	**0.036**	0.536	0.181	0.393	0.960
	N	178	**147**	154	81	**68**	69	97	79	85
BMI	Correlation	-0.015	0.018	0.033	0.076	-0.076	0.146	-0.043	0.186	-0.127
	Sig(2-tailed)	0.848	0.833	0.684	0.500	0.548	0.232	0.693	0.124	0.257
	N	167	134	151	81	64	69	86	70	82
Waist circumference	Correlation	-0.122	-0.072	0.019	-0.034	-0.059	-0.051	-0.078	-0.031	-0.183
	Sig.(2-tailed)	0.102	0.383	0.811	0.764	0.631	0.676	0.445	0.781	0.091
	N	181	150	156	82	69	70	99	81	86
Creatinine	Correlation	**-0.165***	-0.125	0.073	-0.092	-0.224	-0.159	-0.010	0.066	**-0.257***
	Sig.(2-tailed)	**0.033**	0.144	0.390	0.438	0.077	0.218	0.927	0.573	**0.022**
	N	**167**	138	141	74	63	62	93	75	**79**
HbA_1c	Correlation	**-0.351****	**-0.234****	**0.603****	-0.121	-0.064	-0.017	0.167	0.132	-0.028
	Sig.(2-tailed)	**0.000**	**0.004**	**0.000**	0.277	0.601	0.887	0.097	0.246	0.802
	N	**182**	**148**	**153**	82	69	70	100	79	83
FPG	Correlation	**-0.193***	-0.081	**0.382****	-0.108	0.017	0.106	0.099	0.038	0.043
	Sig.(2-tailed)	**0.012**	0.337	**0.000**	0.352	0.897	0.401	0.343	0.742	0.700
	N	**170**	141	**146**	76	64	65	94	77	81
Total cholesterol	Correlation	-0.039	**0.210***	0.057	-0.109	0.183	-0.140	0.077	**0.260***	0.045
	Sig.(2-tailed)	0.632	**0.021**	0.525	0.382	0.195	0.307	0.484	**0.031**	0.709
	N	151	**121**	127	67	52	55	84	**69**	72
LDL-C	Correlation	0.025	0.133	0.126	0.010	0.062	**-0.272***	**0.294****	**0.309****	0.167
	Sig.(2-tailed)	0.745	0.110	0.128	0.930	0.619	**0.026**	**0.004**	**0.006**	0.136
	N	173	145	148	78	66	**67**	**95**	**79**	81
HDL-C	Correlation	-0.025	0.014	-0.132	-0.118	-0.001	0.044	-0.075	-0.084	-0.215
	Sig(2-tailed)	0.745	0.873	0.115	0.305	0.993	0.723	0.484	0.472	0.061
	N	168	141	143	78	66	66	90	75	77
TG	Correlation	0.004	0.087	**0.214****	0.204	0.068	0.156	-0.026	0.200	**0.298****
	Sig.(2-tailed)	0.962	0.300	**0.009**	0.073	0.590	0.216	0.798	0.077	**0.007**
	N	174	144	**147**	78	65	65	96	79	**82**
OXT	Correlation	1.000	**0.321****	**-0.377***	1.000	0.067	0.078	1.000	0.195	0.074
	Sig.(2-tailed)	.	**0.000**	**0.000**	.	0.612	0.541	.	0.085	0.508
	N	182	**138**	**147**	82	59	64	100	79	83
Omentin-1	Correlation	**0.321****	1.000	**-0.309****	0.067	1.000	0.163	0.195	1.000	-0.106
	Sig.(2-tailed)	**0.000**	.	**0.001**	0.612	.	0.252	0.085	.	0.382
	N	**138**	151	**121**	59	69	51	79	82	70
Irisin	Correlation	**-0.377****	**-0.309****	1.000	0.078	0.163	1.000	0.074	-0.106	1.000
	Sig.(2-tailed)	**0.000**	**0.001**	.	0.541	0.252	.	0.508	0.382	.
	N	**147**	**121**	156	64	51	70	83	70	86

[a] Percent within total. [b]*p*-value by independent-sample t-test, and [^]by Chi-square test.

BMI: body mass index (Kg/m2), DBP: diastolic blood pressure (mmHg), SBP: systolic blood pressure, FPG: fasting plasma glucose (mg/dL), HbA1c: hemoglobin glycosylated A1C (%), HDL-C: high density lipoprotein (mg/dL), LDL-C: low density lipoprotein (mg/dL), TG: triglyceride (mg/dL), OXT (oxytocin): (pg/mL), omentin 1 and irisin: (ng/mL), serum creatinine and total cholesterol (mg/dL); Waist circumference (cm); SD: standard deviation.

* Variation is significant at the 0.05 level (2-tailed).

** Variation is significant at the 0.01 level (2-tailed).

Table 5. Comparison between the results of OXT in Current study to the facts in the literatures

Parameters Mean±SD or median-IQR	Qian *et al*.,[17]		P-value	Gürsoy *et al*., [20]		P-value	Current study		P-value
	T2DM-obese	Normoglycemic-obese		Newly diagnosed T2DM	Controls		METS-pre/T2DM	METS-Controls	
Age (years)	46.19±11.06	45.21±9.24	0.287	52.8 ± 10.7	54.7 ± 8.2	NS	51.95±10.97	50.49±9.84	0.332
Gender N (male/female)	46 (28/18)	42 (29/13)	-	80 Zero males	40 Zero males		103 (35/68)	92 (29/63)	0.715
BMI (kg/m^2)	27.49±2.03	27.78±2.66	-	**30.5 ± 4.8**	**28.1 ± 5.7**	**<0.01**	33.51±5.93	33.12±4.97	0.633
SBP (mmHg)	128.39±14.48	128.93±16.03	0.190	**136.2 ± 19.5**	**22.6 ± 17.2**	**<0.01**	**139.66±18.50**	**133.07±17.57**	**0.012**
DBP (mmHg)	**79.72±6.36**	**82.64±12.67**	**0.036**	**86.2 ± 17.9**	**79.0 ± 6.9**	**<0.03**	**82.39±11.87**	**78.66±10.09**	**0.021**
Waist circumference (cm)	94.03±4.21	96.02±9.53	0.392				106.33±13.18	103.34±11.22	0.092
HbA_1c (%)	**9.25±1.91**	**5.34±0.31**	**< 0.001**	**8.7 ± 2.6**	**5.6 ± 0.3**	**<0.01**	**7.05±7.61**	**5.35±0.56**	**0.034**
FPG (mg/dL)	**175.68±49.68**	**90.18±8.28**	**< 0.001**	**199.5 ± 80.7**	**88.0 ± 16.2**	**<0.01**	**119.11±28.89**	**101.29±17.56**	**<0.001**
Total cholesterol (mg/dL)	197.21±45.24	176.33±25.52	0.058	**226.6 ± 70.1**	**185.5 ± 37.2**	**<0.01**	200.24±42.12	196.76±45.15	0.617
LDL-C (mg/dL)	128.38±39.82	111.36±23.58	0.051	132.8 ± 47.2	110.8 ± 32.7	<0.09	136.22±36.39	126.72±38.73	0.086
HDL-C (mg/dL)	**41.37±7.34**	**46.79±12.37**	**0.048**	45.7 ± 11.4	46.0 ± 9.2	NS	44.57±13.05	49.92±24.43	0.066
TG (mg/dL)	**231.17±25.77**	**157.66±82.37**	**< 0.001**	**243.8 ± 58.3**	**140.2 ± 69.2**	**<0.01**	167.59±92.57	151.82±87.79	0.237
OXT (pg/mL)	7.2 (6. 5~8.8)	9.2 (8.2~10.4)	**< 0.001**				**1115.51±540.87**	**2126.87±943.65**	**<0.001**
Omentin-1 (ng/ml)				**307.9 ± 153.1**	**461.0 ± 153.2**	**<0.001**	**3.48±6.58**	**5.81±5.84**	

However the causal relationship between changes in circulating biomarkers levels and the development of T2DM and obesity cannot be excluded. Serial changes in plasma OXT need to be considered at different points of time throughout the day according to the daily and pulsatile patterns of OXT release. A number of acute stresses that could be experienced by the individual subjects may affect plasma OXT levels. Our inclusion criteria to obtain patients with Mets who are newly diagnosed with T2DM or drug-naïve are very difficult. Normal subjects (normoglycemic-normal body weight) were not recruited as a 3rd group of control participants besides the Mets-population. We did not have details of patients' medications. Therefore, we could not exclude the effect of statins, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers on Mets-biomarkers.

Our study is the first clinical study which examined the correlation of Mets-biomarkers (omentin-1 and irisin) and OXT. Our study was powered enough and recruited a large study sample pool which helps to observe all the possible correlations of metabolic biomarkers and clinical parameters. We had studied the relation of OXT with two biomarkers (omentin-1 and irisin). We also studied the correlations of clinical parameters among Mets- pool of participants and both study groups. The gender-based variations in clinical parameters as well as the metabolic biomarkers were clearly stated in our Mets-pool of recruits.

Conclusion

Based on this study we report the proportional correlation of the metabolic neuropeptide hormone OXT and the inflammatory marker omentin-1, and as well as the reciprocal relation of OXT and irisin. Our study cannot rule out any potential molecular

crosstalk of OXT, omentin-1 or irisin in the pathophysiology of metabolic syndrome and its related dysregularities. Taken together, both biomarkers considered as metabolic risk factors, may also serve as putative diagnostic and/or surrogate prognostic tools for metabolic anomalies prediction/prevention and pharmacotherapy.

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دراسة العلاقة بين مستويات هرمون الأوكسيتوسين وبروتين الأومينتين–1 وبروتين الأريسين في بلازما الدم لدى مرضى النوع الثاني من السكري والذين يعانون أيضاَ من الاضطراب الأيضي في الأردن: دراسة مسحية

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الملخص

في هذه الدراسة المسحية تمت مشاركة 92 مريضاً يعانون من متلازمة الاضطراب الأيضي فقط، و103 مريضاً يعانون من متلازمة الاضطراب الأيضي بالإضافة إلى مرحلة ما قبل السكري أو السكري من النوع الثاني، (مع تشابه العمر ومؤشر كتلة الجسم بين المجموعتين). وقد تم استخدام تقنية الإلايزا (مقايسة الممتز المناعي المرتبط بالإنزيم) لقياس مستويات الأوكسيتوسين والأريسين والأومينتين–1 في البلازما.

إن متوسط مستويات الأوكسيتوسين ($p<0.001$) والأومينتين–1 ($p<0.019$) كان أعلى في مجموعة المرضى الذين يعانون من متلازمة الاضطراب الأيضي فقط بالمقارنة مع المرضى الذين يعانون من متلازمة الاضطراب الأيضي بالإضافة إلى مرحلة ما قبل السكري أو السكري من النوع الثاني. وبالعكس فإن تركيز الأريسين في البلازما كان أقل بشكل واضح في المجموعة المذكورة أولاً مقارنة بالمجموعة المذكورة ثانياً ($p<0.001$). في العينة الكلية من المرضى ارتبط مستوى الأوكسيتوسين عكسيا مع مستوى الأريسين وطردياً مع مستوى الأومينتين–1 (معامل ارتباط سبيرمان = $p<0.001,-0.377$) بالنسبة للأريسين و(معامل ارتباط سبيرمان = $p<0.001,0.321$) بالنسبة للأومنتين–1. كما وارتبط مستوى الأومنتين–1 عكسيا مع مستوى الأريسين (معامل ارتباط سبيرمان= $p=0.001,-0.309$).

هذه النتائج تشير بوضوح على أنه يمكن استخدام الأومنتين–1 والأريسين، تماما مثل الأوكسيتوسين، كمواد دوائية لعلاج السمنة ومرض السكري.

الكلمات الدالة: الاوكسيتوسين، الاضطراب الايضي، الأوكسيتوسين والأريسين، و–الأومينتين، مرضى السكري 2، تقنية الانزيمات المصنعة ارتباطيا، المؤشرات الإلتهابية.