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Correlates of Increased Chemerin but Reduced Oxytocin with Adiposity and Atherogenecity Indices in Metabolic Syndrome Patients

Oneassa S. Al-Neimat[1,2], Violet Kasabri[1]*, Randa Naffa[2], Amal Akour[1], Mousa Abu Jbara[3], Yasser Bustanji[1,4]

[1.] School of Pharmacy, The University of Jordan, Queen Rania Street, Amman 11942, Jordan.
[2] School of Medicine, The University of Jordan, Queen Rania Street, Amman 11942, Jordan.
[3.] National Center for Diabetes, Endocrinology and Genetics, Queen Rania Street, Amman 13165, Jordan.
[4.] Hamdi Mango Research Center for Scientific Research, The University of Jordan, Amman 11942, Jordan.

ABSTRACT

OBJECTIVES: the neurohypophysial hormone Oxcytocin (OXT) and an adipokine Chemerin have got a growing evidences about their roles in metabolic syndrome (MetS) and type 2 diabetes (T2DM). we aimed to compare and correlate OXT and Chemerin plasma levels with each other as well as conicity index (CI), waist circumference (WC), waist-to-hip (WHR) ratio, and body mass index (BMI), lipid profile, atherogenicity index (TG/HDL-C ratio), red cell distribution width (RDW) and mean platelet volume (MPV). **METHODS:** in this cross-sectional study, 30 normoglycemic lean subjects (control), 30 normoglycemic (MetS) and 29 newly diagnosed (MetS-Pre/T2DM) candidates were enrolled. Plasma Chemerin and OXT were analyzed by colorimetric-enzymatic assay. **RESULTS**: chemerin (ng/mL) plasma levels significantly higher in MetS and MetS-pre/T2DM groups vs. controls' [268.05 (250.83-292.18) and 234.8 (209.25-260.6) vs. 176.7 (161.15-198.2); p< 0.001 and p=0.003, respectively]. The circulating levels of controls'OXT (pg/mL) 4176.6 (2407.13-5243.3) were significantly higher vs. MetS 1975.4 (1522.25-3191.15) or MetS-pre/T2DM 1403 (1033.95-2567.3) groups; p=0.009 and p=0.001, respectively. A higher chemerin and lower OXT levels in MetS group vs. MetS-pre/T2DM ; p= 0.002 p=0.04 respectively. MetS and MetS-pre/T2DM CI, atherogenicity index, WHR, and RDW-CV% were higher (p=0.05) vs. control group. MetS-pre/T2DM's MPV was higher (p=0.015) vs. control group. In the total study population while chemerin directly correlated, OXT inversely correlated with each of BMI, CI, TG/HDL-C ratio, SBP, HbA_{1C} and TG. A significant inverse chemerin-OXT relationship was observed (p=0.003, r= -0.318). **COCLUSION:** our study cannot rule out any potential molecular crosstalk of Chemerin and OXT in the development of MetS and T2DM

Keywords: Type 2 Diabetes Mellitus, Metabolic Syndrome, Oxytocin, Chemerin, Adiposity Indices, Atherogenicity Index.

1. INTRODUCTION

The metabolic syndrome (MetS) is a set of metabolic distortions which peak cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) risks [(1)]. Central obesity, elevated blood pressure, dyslipidemia and/or insulin resistance (IR) are the foundation of the MetS [1]. Abdominal obesity and IR considered a significant factors for CVD that, usually, leads to T2DM[1,2]. A localized inflammation in hypertrophied adipose tissue propagates a systemic chronic low-grade inflammation and a secretion of abnormal levels of adipokines associated with the development of MetS co-morbidities (insulin sensitivity, glucose and lipid metabolism and inflammatory process impairments) [3]. Recently, Chemerin discovered as an adipocytokin, its inactive form binds to the chemokine—like receptor 1 (CMKLR1) after activation by the

* hotice162@gmail.com
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coagulation, fibrinolytic and inflammatory cascades[4] plays a vital role in adipocyte differentiation and development, and it may act as a modulator of different metabolic pathways in mature adipocyte [5]. Interestingly, chemerin was found to promote the adipogenic differentiation potential[6] and alter the myoblast cell fate from myogenesis to adipogenesis [7]. Moreover, chemerin associates with several metabolic syndrome markers, such as, TG, blood pressure, and insulin resistance [8,9]. Chemerin was evidently found to be a pronounced link between obesity and atherosclerosis [10]. OXT is a nanopeptide synthesized both centrally and peripherally. In parallel to its neuropsychiatric roles, a line of evidence suggests an important role of OXT and its analoges in the obesity, diabetic and Mets [11, 12]. OXT receptor is found to be present in various tissues, including pancreas and adipose tissue [13]. It has been suggested OXT alters adipokin leptin to induce an inhibitory effect on CCK [14] and affect the OXT receptor presenting adipocytes [13]. In this study, the conjoint impacts of both OXT and chemerin on metabolic process give attention to imbue the aim to study the correlation between OXT and chemerin and their link to some metabolic indices in normoglycemic subjects, MetS and T2DM in Jordan. The following indices were evaluated: Adiposity indices (WC, BMI, CI, WHR); Atherogenice index (TG/HDL-C ratio); Inflammatory hematological indices (RDW, MPV).

2. SUBJECTS, MATERIALS AND METHODS

2.1. Study population

Our cross sectional study was conducted in June-December /2016 in diabetes and endocrinology outpatient clinics in the National Center for Diabetes Endocrinology and Genetics (NCDEG) for recruiting the study participants after the approvals from the Scientific Research Committee at the School of Pharmacy, The University of Jordan and the clinical IRB (Institutional Review Board) Committees affiliated NCDEG (101675/9/SM). All procedures performed in this study with human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

2.2. Sample size

Based on the results of Qian *et al.* [(15a)] the sample size was calculated by the formula:

$N= 2*SD^2 (Z_\alpha+Z_\beta)^2 / \Delta^2$ [(15b)] where:

N: Sample size.

Z_α: Type one error= 1.96 when $\alpha = 5\%$.

Z_β: Type two error= 1.28 when $\beta= 10\%$.

fSD = Standard deviation of controls (normoglycemic obese subjects with mean OXT = 9.23 ng/L) and equals 1.14 [(15a)]

Δ = the ambitious difference yielded between the means of case and control pools [(15a)] study equals 9.23-7.16= 2.07 ng/L.

By using the aforementioned equation, the minimal required number of subjects per each study arm = 6 participants.

2.3. Protocol Of Sampling

A total number of candidates (n=177) were assessed for eligibility and according to the study inclusion criteria was 89 individuals aged from18-75 years old consented to participate with a response rate of 69.5% (Figure 1). The diagnosis of MetS was according to the International Diabetes Federation (IDF) criteria [(1)]: if WC with ethnicity specific values was ≥94 cm for men, and ≥ 80cm for women, plus any two of the following risk factors; 1) TG ≥150 mg/dL, 2) HDL-C)<40 mg/dL for men, and <50 mg/dL for women, 3) SBP ≥130 mmHg or DBP ≥85 mmHg, and 4) fasting blood glucose (FBG) ≥100 mg/dL. Recruites were divided into three groups:

1. Control group (n=30): healthy normoglycemic (HbA1C<5.7%, FBS<100mg/dL), lean (19.5< BMI kg/m² < 25), and with absence of any of MetS components;
2. MetS group (n=30): normoglycemic, BMI ≥25 kg/m2 with MetS [(1)].
3. MetS-pre/T2DM group (n=29): prediabetic or T2DM patients [2] with MetS [1] who were newly diagnosed/ antihyperglycemic treatment-naïve.

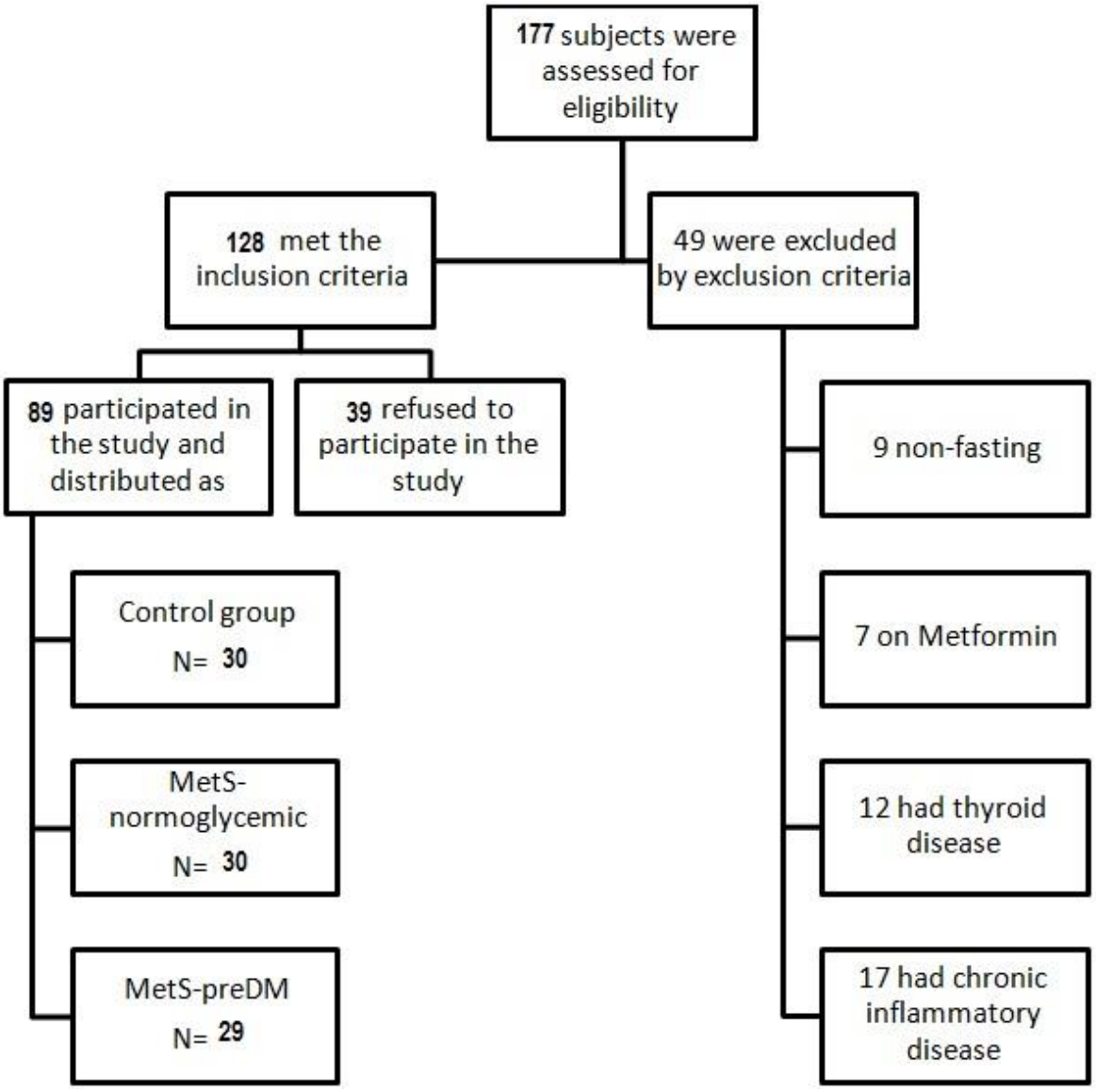

Fig (1): The Recruitment Process Flowchart

Exclusion criteria

- *Not fasting*
- Autoimmune or inflammatory diseases
- Any life-threatening disease
- Endocrine disorder other than MetS or DM
- Previous treatment with an antihyperglycemic agent
- Pregnancy or breast-feeding
- Alcohol or drug abusers

2.3. Data collection

Age, past medical history, Smoking status, gender, weight, height, average of three values of blood pressure (SBP, DBP),WC (measured at midway between iliac crest

and lower ribusing plastic non-stretchable tape without clothing), and hip circumference (HC) (measured at the level of the widest diameter around the buttocks) were obtained from eligible patients by trained researcher. At fasting state (10-12) hrs after meals), blood samples were taken for complete blood count, lipid profile, HbA1C%, FBG, RDW and MPV.

CI was calculated as follows [16]:

$$CI = \frac{WC(cm)}{0.109\sqrt{\frac{Weight(kg)}{Height(m)}}}$$

The kits for both chemerin and OXT were brought from Abcam (USA) and a plate reader of (Bio-Tek Instruments, USA) .The principle of chemerin was sandwich ELISA while of OXT was competitive and analyzed strictly in accordance with the operating instruction of the kit

1.4. Statistical analysis

All data were coded, entered and analyzed using SPSS© 22 (SPSS, Inc., USA). Normality of data had been checked by Shapiro-Wilk test, since some data were not distributed normally so the findings are expressed as median (Interquartile range) (IQR). Chi-Square test was to evaluate inter-group variations in gender distribution. Kruskal-Wallis test was used to check the significant variations in parameters of study between at least 2 continuous groups of data, Mann-Whitney test was used as post – hoc analysis to detect significant differences in continuous variables between each two groups. To compare OXT and chemerin levels between control group and other two groups, log-transformed and MANCOVA was performed to compare their levels to account for age as a covariate. Mann-Whitney test as post –hoc analysis was implemented to detect significant differences of biomarkers levels for gender dimorphism and between MetS and MetS-pre/T2DM as unobvious variation in age between two MetS groups. Spearman's correlation was used as non-parametric test to value the association between continuous variables. The statistical significance were set at P-values <0.05.

3. RESULTS

3.1. Clinical characteristics

Table 2 showed gender was distributed homogenously among the study groups. In perfect alignment with definitive MetS components clustering (WC, SBP, DBP, TG) were significantly higher in the MetS groups (the MetS, the MetS-pre /T2DM), when compared to the control group ($p<0.001$), while no such significant differences between both MetS groups. FBG and HbA1C% were significantly higher in MetS-pre/T2DM arm when compared to both normoglycemic control and MetS arms ($p< 0.001$) which met study inclusion criteria. All adiposity indices, atherogenic index and heamatology indices were significantly higher in MetS groups (the MetS and the MetS-pre /T2DM) when compared to the apparently healthy controls ($P<0.05$) except for MPV where the significance showed for the MetS-pre/T2DM arm ($P<0.05$) (Table 1).

3.2. Biomarker levels

Remarkably, chemerin in MetS arm and MetS-pre/T2DM arm were significantly higher than control group ($p< 0.001$, $p = 0.003$ respectively). Chemerin concentrations were also significantly higher in MetS arm when compared to MetS-pre/T2DM arm ($p= 0.002$) (Table 1). Controls' OXT plasma levels were pronouncedly higher in control group vs. MetS groups (the MetS, the MetS-pre /T2DM) ($p=0.009$, $p=0.001$ respectively). Also, OXT levels were significantly lower ($P < 0.040$) in the MetS-pre/T2DM arm as compared to the MetS arm (Table 1).

Table (1)
Comparison of study parameters

Parameter	Total sample N=89 Median(IQR)	Control group N=30 Median(IQR)	MetS group N=30 Median(IQR)	MetS-Pre/T2DM N=29 Median(IQR)	P1[a]	P2[a]	P3[a]
Gender N (%) * Male Female	34(38.2) 55(61.8)	8(26.7) 22(73.3)	11(36.7) 19(63.3)	15(51.7) 14(48.3)	0.136		
Clinical parameters							
Age (years)	41.5(29-52)	28(22.5-30.5)	46(37.75-54.25)	52(43.5-55)	<0.001	<0.001	0.081
WC (cm)	96(82-105)	79(69-85)	102(93-110)	100(96-107)	<0.001	<0.001	0.755
SBP (mmHg)	135(120-140)	120(115-126.25)	135(127.5-141.25)	140(135-147.5)	<0.001	<0.001	0.065
DBP (mmHg)	80(75-85)	75(70-80)	84(76.5-85.5)	85(77.5-90)	<0.001	<0.001	0.634
FPG (mg/dL)	88(81.5-100.5)	87(79.5-90)	86(79.75-93.25)	112(103-118.3)	0.706	<0.001	<0.001
HbA1c (%)	5.5(5.2-5.7)	5.25(5.1-5.43)	5.4(5.2-5.53)	5.9(5.73-6.8)	0.072	<0.001	<0.001
TG (mg/dL)	148(79.18-210.85)	72(49.25-94.25)	199(156.25-262)	179.5(127.7-242.5)	<0.001	<0.001	0.308
TC (mg/dL)	185.5(150.25-218.05)	169(131.25-209.75)	207(163.5-230.5)	187.9(158.9-254)	0.025	0.058	0.755
LDL-C (mg/dL)	112.45(83.25-147.25)	88(74.25-119)	111.5(84.5-154.98)	130.5(101.7-174.3)	0.026	<0.001	0.228
HDL_C (mg/dL)	40(36-48)	50(44-70.5)	38(34.5-40)	38.4(34.6-42)	<0.001	<0.001	0.571
Adiposity indices and atherogenic index							
BMI (kg/m2)	27.4(23.77-32.755)	22.21(19.93-24.47)	31.17(27.19-35.83)	31.8(27.5-35.2)	<0.001	<0.001	0.705
CI	1.096(0.98-1.17)	0.97(0.87-1.05)	1.15(1.08-1.22)	1.15(1.06-1.18)	<0.001	<0.001	0.458
WHR	0.89(0.825-0.92)	0.82(0.75-0.91)	0.91(0.88-0.93)	0.9(0.87-0.92)	<0.001	0.006	0.144
TG/HDL-C ratio	2.96(1.49-5.62)	1.31(0.94-1.97)	5.105(3.79-6.75)	4.68(2.16-6.55)	<0.001	<0.001	0.255
Hematological indices							
RDW_CV %	13.3(12.53-14.1)	13.1(12.2-13.7)	13.3(12.5-14)	13.6(12.93-14.6)	<0.001	0.011	0.248
MPV(fL)	9.8(8.97-10.53)	9.3(8.55-9.9)	9.9(9.2-10.6)	10.35(9.08-11.03)	0.053	0.015	0.277
Biomarkers							

Parameter	Total sample N=89 Median(IQR)	Control group N=30 Median(IQR)	MetS group N=30 Median(IQR)	MetS-Pre/T2DM N=29 Median(IQR)	P1[a]	P2[a]	P3[a]
Chemirin (ng/mL)	234.05(193.13-267.38)	176.7(161.15-198.2)	268.05(250.83-292.18)	234.8(209.25-260.6)	<0.001*	0.003*	0.002
OXT(pg/mL)	2314(1272.2-4041.55)	4176.6(2407.13-5243.3)	1975.4(1522.25-3191.15)	1403(1033.95-2567.3)	0.009*	0.001*	0.040

a=P value by Mann-Whitney Test

* = P value by MANCOVA

P1=Control group compared to MetS group

P2=Control group compared to MetS-Pre/T2DM

P3=MetS group compared to MetS-Pre/T2DM

CI: conicity index, WC: waist circumference, WHR: waist to hip ratio, TG/HDL-C ratio: triglyceride to high density lipoprotein cholesterol, RDW CV%,: red blood cell distribution width, MPV: mean platelet volume

3.3. Biomarker correlations

In the whole population, chemerin correlated proportional to each of WC, SBP, DBP, HbA1c, TG, TC, BMI, CI, WHR and TG/HDL-c ratio. Meanwhile it inversely related with both HDL-c and OXT.

Empirically OXT correlated negatively with each of WC, SBP, FBG, HbA1c, TG, BMI, CI, and TG/HDL-c ratio. Both parameters did not have any statistically substantial correlations with hematological indices (Table 2). Obviously controls' RDW correlated negatively with chemerin while the BMI and TG correlated positively. OXT had not any correlations to show (Table 2). Evidently chemerin correlated proportionally with each of BMI, WC, CI, TG/HDL-C ratio but correlated inversely with LDL-C in the MetS arm. Of note OXT associated negatively with WHR (Table 2). The MetS-pre/T2DM group failed to show significant correlations for both biomarkers.

Table (2)
Chemerin and OXT correlations

Parameter(s)	Correlations	Total population		Control Group		MetS-Group	
		Chemerin (ng/mL)	**OXT**(pg/mL)	**Chemerin**(ng/mL)	**OXT**(pg/mL)	**Chemerin**(ng/mL)	**OXT**(pg/mL)
Clinical parameters							
Age (years)	R	0.567**	-0.292**	-0.072	0.200	0.295	0.227
	Sig (2-talied)	0.001	0.007	0.709	0.307	0.113	0.236
WC(cm)	R	0.641**	-0.291**	0.308	-0.301	-0.498**	-0.314
	Sig (2-talied)	0.001	0.007	0.104	0.120	0.006	0.103
SBP(mmHg)	R	0.475**	-0.330**	0.038	0.186	0.147	-0.055
	Sig (2-talied)	0.001	0.002	0.846	0.343	0.438	0.778
DBP(mmHg)	R	0.294**	-0.130	0.156	0.121	-0.129	0.018
	Sig (2-talied)	0.005	0.236	0.419	0.540	0.496	0.928
FPG(mg/dL)	R	0.106	-0.234-*	0.289	0.236	-0.235	-0.136
	Sig (2-talied)	0.336	0.036	0.129	0.226	0.211	0.482
HbA1c(%)	R	0.238*	-0.274-*	-0.123	0.076	-0.042	-0.078

Parameter(s)	Correlations	Total population		Control Group		MetS-Group	
		Chemerin (ng/mL)	**OXT**(pg/mL)	**Chemerin**(ng/mL)	**OXT**(pg/mL)	**Chemerin**(ng/mL)	**OXT**(pg/mL)
	Sig (2-talied)	0.026	0.012	0.525	0.699	0.827	0.687
TG(mg/dL)	R	0.646**	-0.257-*	0.406*	0.073	0.289	0.080
	Sig (2-talied)	0.001	0.018	0.029	0.711	0.122	0.679
TC(mg/dL)	R	0.237*	-0.171	0.093	0.012	-0.110	0.152
	Sig (2-talied)	0.029	0.125	0.632	0.952	0.571	0.441
LDL-c(mg/dL)	R	0.189	-0.210	0.121	-0.029	-0.362*	0.182
	Sig (2-talied)	0.079	0.055	0.533	0.884	0.049	0.345
HDL-c(mg/dL)	R	-0.524-**	0.191	-0.103	-0.046	-0.192	0.167
	Sig (2-talied)	0.001	0.085	0.593	0.818	0.319	0.397
Adiposity indices and atherogenic index							
BMI(kg/m²)	R	0.644**	-0.333-**	0.613**	-0.009	0.424*	-0.189
	Sig (2-talied)	0.001	0.002	0.001	0.962	0.020	0.327
CI	R	0.618**	-0.250-*	0.077	0.185	0.548**	-0.059
	Sig (2-talied)	0.001	0.021	0.690	0.346	0.002	0.760
WHR	R	0.380**	-0.206	0.218	0.122	0.129	-0.387*
	Sig (2-talied)	0.001	0.058	0.256	0.537	0.498	0.038
TG/HDL-c ratio	R	0.683**	-0.258-*	0.331	0.052	0.444*	-0.117
	Sig (2-talied)	0.001	0.019	0.080	0.792	0.014	0.545
Hematological indices							
RDW(%)	R	0.103	-0.077	-0.454*	0.147	0.152	0.296
	Sig (2-talied)	0.352	0.495	0.015	0.463	0.449	0.135
MPV(fL)	R	0.170	-0.107	-0.112	-0.049	0.077	0.177
	Sig (2-talied)	0.132	0.350	0.571	0.807	0.701	0.376
Biomarkers							
Chemerin(ng/mL)	R	1.000	-0.318-**	1.000	-0.039	1.000	0.111
	Sig (2-talied)		0.003		0.844		0.568
OXT(pg/mL)	R	-0.318-**	1.000	-0.039	1.000	0.111	1.000
	Sig (2-talied)	0.003		0.844		0.568	

Spearman's correlations R=Correlation coefficient. Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2-tailed). BMI: body mass index, systolic blood pressure, DBP: diastolic blood pressure FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin (A1c), TG: triglycerides, TC: total cholesterol, LDL-C: low density lipoprotein, HDL-C: high density lipoprotein. CI: conicity index, TG/HDL-C ratio: triglyceride to high density lipoprotein cholesterol, CI: conicity index, WC: waist circumference, WHR: waist to hip

3.4. Gender dimorphism of OXT and Chemerin levels

Figure 2 shows the lack of gender dimorphism of either biomarker in each study arm (Fig 2).

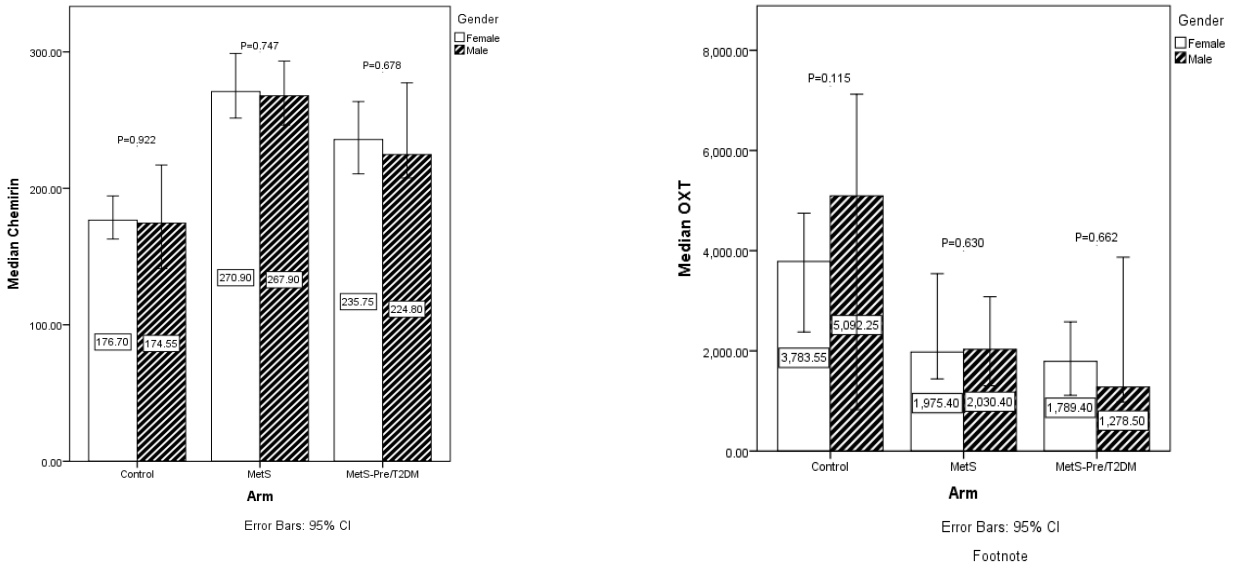

Fig (2): Intra-group Gender dimorphism comparison of circulating levels of metabolic biomarkers in study arms.

Results are presented as median –IQR , P value by Mann-Whitney Test.

4. DISCUSSION

An increased prevalence of MetS worldwide and among Jordanian adults with increased WC (71.6%) and hypertriglyceridemia (50.2%) increases the risk of T2DM [17]. In the view of a previous studies of OXT and chemerin associations with MetS and diabetic components, the aim of our work was to evaluate the clinical utility of plasma OXT and chemerin as a marker of MetS and type 2 diabetes and to investigate its correlation with clinical and laboratory parameters of these conditions. Besides easily obtainable, a possible useful tools as a good markers and predictors of metabolic, type 2 diabetes and cardiovascular diseases , herein , BMI, CI, WHR [18], TG/HDL-C ratio [19], RDW and MPV levels [20] are studied. In best of our knowledge, this is the first study which is conducted in these three groups in one study according to the recently updated guidelines [1-2] with restricted criteria of normal BMI for control group, MetS with normoglycemic patients and a antihyperglycemic naive patients in MetS-pre/T2DM.

4.1.Chemerin levels

Our results identified a significant increase in plasma chemerin levels in MetS arm as compared to the control group and MetS-Pre/T2DM arm. Besides significant increase in plasma chemerin levels in MetS-PreT2DM arm as compared to the control group. Our results are consistent with previous studies reporting that chemerin is significantly increased in T2DM as compared with non-diabetic subjects[20-23] except for Takahashi study where chemerin levels significantly higher in control group than chronic T2DM group [20] which may explained by some diabetic medication intake decreases chemerin levels [(24)]. On other hand, other studies reported a significantly increased chemerin levels in MetS as compared with control group [9, 22, 23, 25, 26] .Our results were in line with earlier reports of Takahashi et al. [20] and in a regional countries [22] that chemerin levels were significantly increased in MetS as compared with T2DM. Notably, it was not obvious whether normal BMI is a characteristic [23, 26] or not determined [22] for the control subjects in the previously mentioned studies as the obesity has an impact

on chemerin levels [27-28]. Besides, the differences in studies inclusion criteria of groups (the control, the MetS, the T2DM) and lipid profile. Taken together, it has not definitely established if there a compensatory effect of increased chemerin specifically in MetS arm, or if the high levels of glucose in MetS-Pre/T2DM arm impair the chemerin secretion by adipocyte dysfunction with; a decrease in MetS-Pre/T2DM when compared to MetS arm. But it may serve as an independent marker in diagnosis MetS or T2DM.

4.2.Chemerin correlations

Our study has show that chemerin levels correlated with parameters of MetS and T2DM in consistency with previous studies' findings. It was reported that chemerin levels significantly and positively correlated with age [23,26], WC, BMI, FBG [23,25,27],WHR [25,27],HbA1c, SBP [23,25], DBP[(27)],TG [23,26-27] ,TC and LDL-C[27] but negatively with HDL-C [23,25]. Tahakashi et al study reported a disagreement of a significant negative association with FBG and HbA1c[20]. This may be due to taking anti-diabetic drugs by T2DM group [24] . In addition to these correlations, our study shows significant positive correlations of chemerin levels with CI and TG/HDL-C ratio but absence of such correlations with RDW and MPV, which was not labeled in literature. Our study has showed that chemerin levels associated with TG levels regardless of the absence MetS components in control group. On the one hand, chemerin levels associated with BMI suggesting that chemerin may also be considered a risk factor of development MetS and/or an ongoing pro-inflammatory state in these subjects with underestimate underlying body fat or metabolic status. Moreover, maybe subjects with TOFI (thin outside, fat inside) [29] or sarcopenic obesity in control group can be with a future risk of developing insulin resistance and MetS which may be explained by reduced physical activity or diet style [30] and decreased myogenesis with induction of adipogenisis [7].

It was reported that low RDW related to higher TG levels and WC showed a higher risk of diabetes developing in healthy subjects [31]. Another study shows a higher prevalence of MetS but lower prevalence of high levels of TG (≥150 mg/dL) in subjects with higher RDW (≥ 14%) [32;] This may explain our study results of the negative correlation of chemerin with RDW besides chemerin's positive correlations with TG and BMI in control group. In view of our study findings, increased chemerin levels in control group with normal BMI suggestively reveals an increased risk of developing MetS or T2DM.The normal BMI and TG numbers may mask an ongoing low grade inflammation. This signifies the future determination of chemerin cutoff point and correlation with visceral obesity studies to help investigating the value of chemerin as biomarker in such apparently healthy individuals at risk for metabolic dysfunction. Interestingly, our study reveals a significant negative LDL-C - chemerin correlation beside significant positive correlations of chemerin with each of BMI, WC, CI and TG/HDL-C ratio in MetS group. Increased circulating TG leads to increasing large VLDL levels thus generating LDL-C particles enriched with TG with misleading numbers of small dense LDL-C particles [32-35]. In effect LDL-C can be quite an inappropriate indicator of cholesterol levels and the consequences of MetS while TG/HDL-C ratio stands out as a good indicator of these risks [18].

4.3.Gender-based dimorphism in chemerin levels outcomes in present study compared with previous studies

In a striking dissimilarity to our findings; Takahashi, et al. [20] described the chemerin levels significantly higher in male (n=66) than in female (n=22) control subjects ($p <$ 0.005). Nevertheless Weigert, et al. [36] report demonstrated that plasma chemerin levels were similar in females and in males in T2DM group chemerin (ng/mL) in females and in males (156 (33–425) vs. 140 (43–312)**)**, indicating that there is no gender dimorphism at least in these patients,**.** Likewise, Stejskal, et al. [(9)] reported the lack of statistically significant difference in chemerin levels median (μg/L) (167 vs. 209) between men and women in a group of healthy volunteers (n = 55, 26 men, 24 women).

4.4. OXT levels

Regarding results of OXT levels, our study identified

that controls' OXT plasma levels were higher as compared to MetS groups (MetS, and MetS-pre/T2DM). Moreover, OXT levels were significantly lower in MetS-pre/T2DM arm than in MetS arm. Our findings were comparable to the results of a previous Jordanian studies in MetS-pre/T2DM patients, the OXT levels were significantly lower as compared to those with MetS-Normoglcemic patients [37] .Qian, et al. [38] study reported a significantly lower OXT levels in obese patients with T2DM, when compared to those lean with normal glycemic tolerance (NGT) [38]. Yuan, et al. [39] a chine's study, showed the OXT levels in non-MetS group were significantly higher than the MetS group, even the clinical characteristics FBG, HbA1c and 2hPG of the non-MetS group were at least in a prediabetes rang levels [39]. Interestingly, in a recent study serum OXT levels were founded significantly lower in obese children than in non-obese, and lower in obese children with MetS than to those without [40]. These lines of evidence suggest a link of OXT regulation with metabolic dysfunction which could be impact by central/peripheral action.

4.5.OXT correlations

Qian, et al. [38] and Yuan, et al. [39] studies supported our findings in total pool of sample where OXT inversely correlated with BMI, HbA_{1c}, FPG and TG and not with DPB and HDL-C. Besides, a consistent with ours was obtainable with Yuan, et al. [39] findings where OXT insignificantly correlated with TC and LDL-C. The present study revealed an inverse correlation of OXT with WC and SBP while in both previous studies was not significantly correlated [38]. Moreover, AL-Rawashdeh, et al. [37] study could only demonstrate OXT's reciprocal association with both HbA_{1c} and FPG. The present study revealed an inverse correlation of OXT with each of CI and TG/HDL-C ratio while the previous studies didn't conduct these correlations. Our study revealed significant link of OXT level with almost all of MetS picture. OXT - WHR significant correlation was ascribed to MetS arm.

Importantly Qian, et al. [38] reported the lack of significant variation between OXT levels in females vs. those of males (8.90 (7.13–10.15) vs. 8.69 (7.32–9.77), ng/L; (P =0.864)). In addition, baseline plasma OXT levels did not vary significantly among healthy men (1.5 ± 0.2 μU/mL), nonpregnant women (1.4 ± 0.2 μU/mL), or pregnant women before labor (1.3 ± 0.1 μU/mL) and did not differ in an additional subgroup of 20 women receiving oral contraceptive medication (1.8 ± 0.7 μU/mL) [41]. The variation between studies' findings could be related to uncounted confounding factors such as depressive disorder [42] which impact OXT levels.

4.6. Correlations between plasma levels of OXT and chemerin

A negative correlation was reported between OXT and chemerin levels in the total pool of the study participants (p=0.003, r= -0.318). Individuals with low circulating OXT levels coupled with high chemerin levels were at significantly increased risk of MetS and of T2DM as both were significantly correlated with MetS components and adiposity indices (Fig 3). Taken together, these findings provide a strong evidence of chemerin and OXT effect on cardiovascular diseases, atherosclerotic disorders and glucose profile disturbances at least in Jordanian MetS and pre/diabetic patients. Our study group was recruited at the NCDEG which would representative for the Jordanian population. Taken for metabolic risk factors; the combination of both markers could provided a theoretical basis and better understanding for the etiology of MetS and T2DM from the aspect of the metabolic distortions factors in which the incidence of MetS and T2DM can be well controlled. Future studies with larger sample are needed to value the useful of both diagnostic/prognostic tools for prediction of MetS and T2DM high risk patients.

CONFLICT OF INTEREST The authors declare none.

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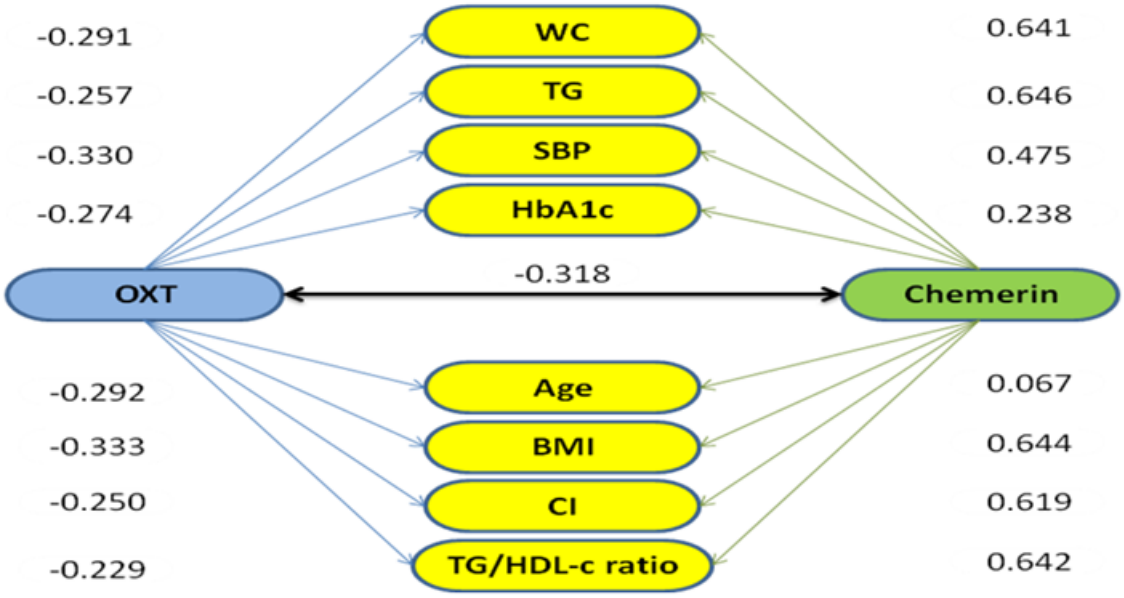

Fig (3): Cross sectional Correlations between OXT, Chemerin and Clinical Parameters in whole study population

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علاقة زيادة الكيمرين وانخفاض الاكستوسين مع مؤشرات السمنة والشحوم الأيضية عند مرضى متلازمة اضطراب الأيضي

اونيسه سند النعيمات [١،٢]، فيوليت كسابري [١]*، رندا نفاع [٢] ، أمل العكور [١]، موسى ابو جباره [٣]، ياسر البستنجي [١،٤]

[١] كلية الصيدلة، الجامعة الاردنية، شارع الملكة رانيا، عمان ١١٩٤٢، الأردن.

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[٣] المركز الوطني للسكري والغدد الصماء والامراض الوراثية، شارع الملكة رانيا، عمان ١٣١٦٥، الأردن.

[٤] مركز حمدي منكو للأبحاث، الجامعة الاردنية، عمان ١١٩٤٢، الأردن.

ملخص

الأهداف: ظهرت أدلة متزايدة حول دور الهرمون النخامي العصبي الأوكسيتوسين والبروتين الدهني الجاذب الكميرين في متلازمة الاضطراب الايضي والنوع الثاني من السكري. وقد هدفت هذه الدراسة إلى تحقيق الترابط بين مستوى بلازما لكل من الأوكسيتوسين والكيمرين وكذلك مؤشر سمنة الخصر، ومحيط الخصر، نسبة محيط الخصر الى محيط الورك، ومؤشر تصلب الشرايين (نسبة الدهون الثلاثية م الثلاثية إلى البروتين الدهني العالي الكثافة ا)، وقياس توزيع كريات الدم الحمراء ومعدل حجم الصفائح الدموية.
الطرق: في دراسة مسحية، ٣٠ شخص لديهم مستوى السكر والدهون طبيعي (المجموعة ١)، ٣٠ مريض مع متلازمة الاضراب الايضي (المجموعة ٢)، ٢٩ مريض مع متلازمة الاضطراب الايضي مع ما قبل السكر/ السكري النوع ٢ (المجموعة ٣)، حيث أنهم كانوا متطابقين من حيث مؤشر كتلة الجسم (والجنس والعمر. وقد تم قياس الأوكسيتوسين والكيمرين في البلازما عن طريق الفحوصات اللونية الأنزيمية. وقد تم فحص الارتباط بين هذه المؤشرات الحيوية الأيضية، وكذلك مؤشرات السمنة والمؤشرات الدموية للمشاركين في الدراسة.

النتائج: ان مستويات الكيميرين كانت أعلى في المجموعة (٢، ٣) مقارنة بالمجموعة (١). مستويات الاكسيتوسين عند المجموعة (١) أعلى مقارنة بالمجموعة (٢،٣). ووجد أن أعلى مستوى للكيمرين واقل مستوى للاكسيتوسين لدى المجموعة ٢ مقارنة بالمجموعة ٣. بالاضافه إلى انه في مجموعتي (٢) و(٣) كان فيها (مؤشر تصلب الشرايين، ومؤشر سمنة الخصر وقياس توزيع كريات الدم الحمراء، ومحيط الخصر، ونسبة محيط الخصر الى الورك) اعلى بكثير($p>.05$) مقارنة مع مجموعة رقم (١). من المثير للاهتمام ان معدل حجم الصفائح الدموية في مجموعة (٣) كان اعلى بشكل جوهري ($p=0.015$) مقارنة بجموعة (١). وفي مجموع عينات الدراسة وجد ان الكيمرين يتناسب طرديا والاكسيتوسين يتناسب عكسيا مع مؤشر سمنة الخصر، الضغط الانقباضي، الهيموجلوبين السكري التراكمي، ومؤشر تصلب الشرايين (نسبة الدهون الثلاثية م الثلاثية إلى البروتين الدهني العالي الكثافة ا) والدهون الثلاثية. وكذلك وجدت علاقة عكسية بين مستويات الاكسيتوسين والكيمرين ($p=0.003, r= -0.318$)).

الخاتمة: لا تستطيع دراستنا استبعاد أي تداخل محتمل بين الاكسيتوسين والكيمرين في تطور متلازمة الاضطراب الايضي والنوع الثاني من السكري.

الكلمات الدالة: داء السكري من النوع الثاني ، متلازمة الأيض ، الأوكسيتوسين ، الكيميرين ، مؤشرات الشحوم ، مؤشر تصلب الشرايين

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