

## Oxytocin and Cholecystokinin Correlates with Metabolic Syndrome's Atherogenicity and Adiposity Indices

Taiba F. Al-Athami<sup>1,2</sup>, Violet Kasabri<sup>1\*</sup>, Randa Naffa<sup>2</sup>, Amal Akour<sup>1</sup>,

Dana Hyasat<sup>3</sup>, Yasser Bustanji<sup>1,4</sup>

<sup>1</sup> School of Pharmacy, The University of Jordan, Queen Rania Street, Amman 11942, Jordan.

<sup>2</sup> School of Medicine, The University of Jordan, Queen Rania Street, Amman 11942, Jordan.

<sup>3</sup> National Center for Diabetes, Endocrinology and Genetics, Queen Rania Street, Amman 13165, Jordan.

<sup>4</sup> Hamdi Mango Research Center for Scientific Research, The University of Jordan, Amman 11942, Jordan.

\* Corresponding author at: School of Pharmacy, The University of Jordan, Queen Rania Street, Amman 11942, Jordan. hotice162@gmail.com

### ABSTRACT

**OBJECTIVES:** Our study aimed to investigate the correlation between plasma oxytocin (OXT) and cholecystokinin (CCK) as well as conicity index (CI), waist circumference (WC), waist circumference to hip circumference (WHR) ratio, red cell distribution width (RDW\_CV%), mean platelet volume (MPV; fL) and TG/HDL-C ratio in metabolic syndrome (MetS) and Type-2 diabetes mellitus (T2DM) patients. **METHODS:** In a cross-sectional design, 30 normoglycemic lean subjects (control), 30 nondiabetic MetS and 29 MetS-Pre/T2DM subjects were enrolled. Plasma OXT and CCK were measured by colorimetric-enzymatic assay and expressed as median (interquartile range). **RESULTS:** CCK plasma levels (pmol/L) lacked pronounced discrepancy in nondiabetic MetS and MetS-pre/T2DM groups vs. lean -healthy controls (9.67 (7.14 – 13.7) and 6.73 (5.06 – 7.68) vs. 5.2 (2.86 – 7.56); p= 0.129 and 0.708, respectively). OXT plasma concentrations (pg/mL) in both nondiabetic MetS and MetS-pre/T2DM groups were markedly (p<0.05) lower vs. controls' (both 1975.4 (1522.25-3191.15) and 1403(1033.95-2567.3) vs. 4176.6 (2407.13-5243.3) but no inter-MetS groups variations in OXT levels were detected. In addition, the levels of following parameters and indices were substantially (p<0.05) elevated in both MetS and MetS-pre/T2DM groups when compared to healthy -lean controls; (WC; cm) (102(93-110) and (100(96-107) vs. ( 79(69-85)), WHR (0.91(0.88-0.93) and 0.9(0.87-0.92) vs. 0.82(0.75-0.91)), CI (1.15(1.08-1.22) and (1.15(1.06-1.18) vs. (0.97(0.87-1.05)), (RDW; CV%) (13.3(12.5-14) and 13.6(12.93-14.6) vs. 13.1(12.2-13.7)), TG/HDL-C ratio(5.105(3.79-6.75) and (4.68(2.16-6.55) vs. 1.31(0.94-1.97)), while (MPV;fL) was exceptionally higher for MetS-pre/T2DM group (but not for MetS group; p>0.05) when compared to control group (10.35(9.08-11.03), vs. 9.3(8.55-9.9)). **CONCLUSIONS:** in nondiabetic MetS and MetS-pre/T2DM patients; OXT circulating concentrations (unlike CCK) were substantially decreased vs. healthy-lean controls.

**Keywords:** Cholecystokinin; Oxytocin; Conicity Index; RDW and MPV; Blood and Adiposity Indices.

### 1. INTRODUCTION

Diabetes is a complicated, life-long disease requiring

\* hotice162@gmail.com

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regular medical care with multifactorial risk-reduction strategies beside control of glucose blood levels and it is classified into: Type1 diabetes mellitus (T1DM), whose patients are characterized by absence of insulin secretion. In contrast, patients with type 2 diabetes mellitus (T2DM) have relative deficiency in insulin secretion in addition to

insulin resistance (IR) as well as gestational diabetes (GDM).Diagnosis of DM is diagnosed by either fasting blood glucose (>126 mg\dl (7.0 mmol/L)) or glycated hemoglobin (HbA1c) ( $\geq 6.5\%$  (48 mmol/mol)). Prediabetes is the term used for individuals with impaired fasting glucose (IFG) (100-125 mg/dL (5.6–6.9 mmol/L) and impaired OGTT, collectively indicating an increased risk for the future development of diabetes <sup>(1)</sup>. Metabolic Syndrome (MetS) is a group of metabolic abnormalities which confers upon an individual a significant elevation in cardiovascular disease (CVD) risk - approximately twice as high as those without MetS <sup>(2-4)</sup>. The pathogenesis of MetS and its components is not well understood, central obesity and insulin resistance are recognized as causative factors <sup>(2-3)</sup>. Uncontrolled high blood glucose levels can affect the heart and blood vessels, eyes, kidneys and nerves, which lead to microvasuclar and macrovascular complications on long term of the disease <sup>(4)</sup>.

Platelet volume is an indicator of platelet function and activation and can be quantified as mean platelet volume (MPV) by clinical hematology analyzers. It has been found that platelets activity has predictive value for ischemic stroke or coronary arterial diseases in patients with T2DM <sup>(5)</sup>. The red blood cell distribution width (RDW) is a measure of variation in the size of circulating red blood cells (RBCs) and expressed by  $RDW-CV\% = (\text{Standard deviation of red blood cell volume} \div \text{mean cell volume}) \times 100\%$  <sup>(6-7)</sup>. High RDW indicates the presence of anisocytosis which is related to the impairment of erythropoiesis and degradation of RBCs, reflecting chronic inflammation and increased oxidative stress, both of which are signs of T2DM <sup>(6)</sup>. Both RDW and MPV are elevated in patients with MetS and they are becoming more obvious as numbers of the diagnostic criteria of MetS <sup>(7)</sup>.

Anthropometric parameters serve as indicators to visceral and subcutaneous abdominal adipose tissues. They are associated with IR and MetS abnormalities <sup>(8)</sup>. They include: body mass index (BMI) waist circumference (WC) to hip circumference (HC) ratio (WHR). WC is

measured using a non-stretchable standard tape over the unclothed abdomen at the narrowest point between the costal margin and iliac crest. HC is measured over the light clothes at level widest diameter around the buttocks. WC\height (cm) ratio (WHR) and the conicity index (C-index), which is calculated by all of these parameters, are indicators of fat accumulation in the abdomen <sup>(9-10)</sup>. The conicity index (C-index) is calculated by  $[C\text{-index} = \frac{WC(cm)}{109 \sqrt{\frac{bodyweight(Kg)}{height(m)}}}]^{(9)}$ . It had been concluded that severity of IR and presence of coronary atherosclerotic events correlate with TG\HDL-c ratio (Atherogenic index)<sup>(9, 11)</sup>.

Oxytocin (OXT) is a neuropeptide composed of nine-amino acids that are produced by OXT neurons placed in the hypothalamus <sup>(12-15)</sup>. OXT has physiological functions, including laboring and lactation in females. In addition to these functions, it had been found recently that OXT reduces weight, improves lipid profile by decreasing low-density lipoprotein (LDL-c) and increasing high-density lipoprotein cholesterol (HDL-c), and increases both secretion and sensitization of insulin <sup>(12-14)</sup>. Qian *et al.* <sup>(15)</sup> found that concentrations of OXT decreases as BMI, WHR, HbA1c, FPG, total cholesterol (TC), triglycerides (TG) and LDL-c increase .

Cholecystokinin (CCK) is peptide composed of 33 amino acids that are secreted in response to lumen of intestine from endocrine cells that are located in jejunum <sup>(16-18)</sup>. The actions of the CCK are mediated by CCK receptor 1(CCK1R) that can be responsible for CCK role in lowering food intake and CCK receptor 2(CCK2R) that mediates pancreatic control of glucose homeostasis <sup>(19)</sup>. CCK has a beneficial role in slowing the progression of diabetic nephropathy through the suppression of macrophage infiltration in the diabetic kidney by inhibition of nuclear factor κB (NF-κB), which is one of

the essential mediators in inflammatory response. It also plays a significant role in the progression of diabetic nephropathy, since CCK1R and CKK2R are distributed in the kidneys and macrophages<sup>(20)</sup>.

## 1. EXPERIMENTAL

This was a cross-sectional study in which the relationship between the disease and exposure status of a population was determined once at a specific time point<sup>(21)</sup>. Our study sample size was calculated according to the findings of Qian, *et al.*<sup>(15)</sup> and the formula used was  $N = 2 * SD^2 (Z\alpha + Z\beta)^2 / \Delta^2$  where<sup>(22)</sup>:

N: Sample size.

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

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

SD= Standard deviation OXT baseline from Qian, *et al.*,<sup>(15)</sup> study and equals 1.38 ng/L.

$\Delta$  = the difference yielded between OXT levels of diabetic /pre-diabetic group vs. the control group post-3 months treatment was 2.07 ng/L. Using this equation, the required number was 9 patients per each study arm but triple folds were recruited for maximal validity and impact of outcomes. Patients were recruited for one time visit without follow up.

### 1.1. Clinical setting and duration

Approval for the study was obtained from the Clinical IRB (Institutional Review Board) Committees affiliated with National Center for Diabetes, Endocrinology, and Genetics (NCDEG) (101675/9/SM). Informed written consent was obtained from each participant. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards<sup>(24)</sup>. All participants who attended the Diabetes/Endocrinology outpatient clinics at NCDEG for the first time were screened for potential recruitment and for collecting blood samples following signing the informed consent form (ICF) written in Arabic.

### 1.2. Protocol of sampling

The age of participants ranged between 18-75 years old. Our study population is divided into three groups based on values of BMI<sup>(23)</sup>, glycemic parameters of participants<sup>(1)</sup> and the presence of at least 2 components of MetS in addition to central obesity; according to the definition determined by the International Diabetes Federation (IDF)<sup>(3)</sup>.

#### A-Inclusion criteria

Group 1 (Healthy lean control): Normoglycemic (with HbA1c < 5.7% or FPG < 100 mg/dL) and lean with  $19.5 < \text{BMI kg/m}^2 < 25$ .

Group 2 (MetS patients): Non-diabetic subjects as well as overweight of  $\text{BMI} \geq 25 \text{ kg/m}^2$  or obese of  $\text{BMI} \geq 30 \text{ kg/m}^2$  having three or more of the MetS components as delineated by the International Diabetes Federation ((IDF)<sup>(3)</sup>.

Group 3 (MetS-Pre/T2DM patients): Drug naïve newly diagnosed patients with prediabetes or T2DM as well as overweight or obese having three or more of the MetS components as delineated by the International Diabetes Federation ((IDF)<sup>(3)</sup>.

#### B-Exclusion criteria

Interviewed subjects were excluded if they were

- 1)- Pregnant or breast-feeding women;
- 2)- Individuals on any hypoglycemic agents;
- 3)- Individuals with autoimmune or inflammatory or life-threatening diseases;
- 4)- Individuals with obesity secondary to endocrine disorders other than diabetes;
- 5)- Alcohol or drug abusers.

### 1.3. Demographic characteristics and laboratory data of population

For consenting eligible subjects, the demographic and clinical characteristics were collected, including age, weight, height and medical history. MetS components (WC, HC and blood pressure) and laboratory data were as follows: 1)- biochemical tests (HbA1c, FPG and lipid panel (TG, TC, LDL-c and HDL-c); 2)- Automated complete blood count CBC (RDW-CV% and MPV) 3)- CI, WHR, BMI and

TG/HDL-c ratio For interviewed individuals who met the inclusion criteria of the study and signed (ICF), the blood samples in lithium heparin tubes were centrifuged at 0 °C at 2000 round per minute for 10 minutes and the plasma harvested was kept in deep freeze at -80° C in labeled eppendrofs with participants' names and date until analysis.

**1.4. Measurement of Metabolic Biomarkers (OXT and CCK) plasma levels**

Using Enzyme-linked-immunosorbent assay (ELISA) in accordance with manufacturers' protocols; Abcam's (USA) OXT *in vitro* competitive binding ELISA kit is designed for the accurate quantitative measurement of OXT in human plasma. The color generated was read at 405nm on a plate reader (Bio-Tek Instruments, USA). The immunoplate of CCK kit was procured from Phoenix Pharmaceuticals®, INC (USA) and assay. The standard curve was established by plotting the measured optical density at 450nm on a plate reader (Bio-Tek® Instruments, USA).

**1.5. Statistical analysis**

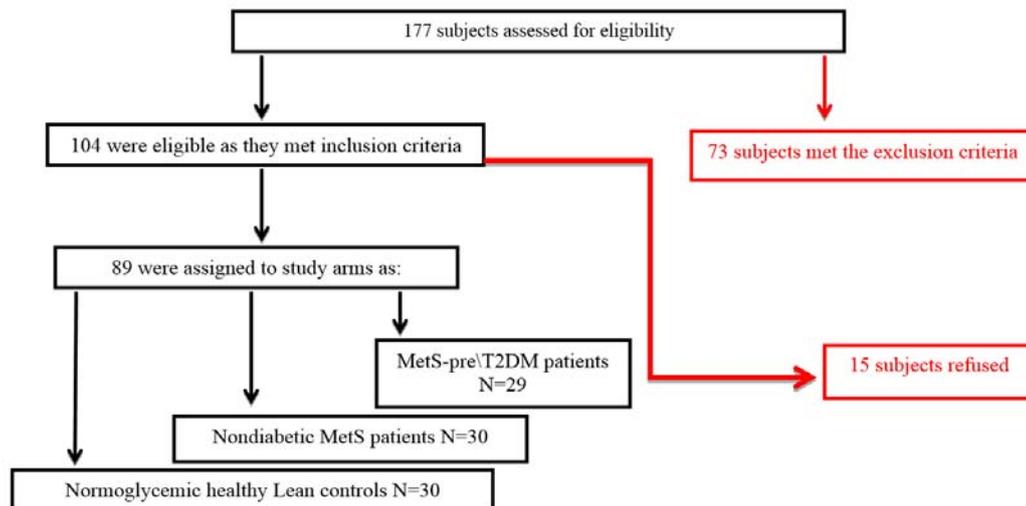
All data were coded, entered and analyzed using SPSS® 22 (SPSS, Inc., USA). Normality of data had been checked by Shapiro-Wilk test and based on findings of this test the findings of our study were expressed as median ± Interquartile range (IQR). Since our data were not

normally distributed, Kruskal-Wallis test was used to check if there were significant variations in parameters of study between at least 2 continuous groups of data. Mann-Whitney tests were implemented. Chi-square test was used to evaluate if there were inter-group significant variations in gender distribution. Multivariate analysis of covariance (MANCOVA) was used to eliminate the effect of age as a covariate on the relationship between the independent groups of variables and the continuous dependent variables. Moreover, Spearman's correlation was used as non-parametric test to estimate the correlation between the two variables.

**3. RESULTS**

**3.1. Study population**

Out of 177 subjects assessed collectively for eligibility, 73 were not basically eligible as they met the exclusion criteria. Among the 104 interviewees who were eligible, 15 potential participants refused participation with a response rate of roughly 86%. Therefore, the total number of participants according to the study inclusion criteria was 89 who were assigned as either nondiabetic (30) or pre/diabetic (29) MetS participants along with the 3<sup>rd</sup> arm of 30 healthy lean controls (Fig 1).



**Figure 1: Study recruitment flowchart**

**Table 1. Demographic, clinical characteristics adiposity and hematological indices and molecular biomarkers in total study population and each group of the study**

Parameter	Total sample N=89 Median (IQR)	Control group N=30 Median (IQR)	MetS group N=30 Median (IQR)	MetS pre/T2DM group N=29 Median(IQR)	P1a	P2a	P3a
Age (Years)a	41.5 (29-52)	28 (22.5-30.5)	46 (37.75-54.25)	52 (43.5-55)	<0.001	<0.001	0.081
BMI (kg/m <sup>2</sup> )a	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
Gender N% <sup>b</sup> 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		
SBP (mm Hg)	135 (120-140)	120 (115-126)	135 (127.5-141.3)	140 (135-148)	<0.001	<0.001	0.065
DBP (mm Hg)	80 (75-85)	75 (70-80)	84 (76.5-85.5)	85 (77.5-90)	<0.001	<0.001	0.634
FBG (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) <sup>a</sup>	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) <sup>a</sup>	40 (36-48)	50 (44-70.5)	38 (34.5-40)	38.4 (34.6-42)	<0.001	<0.001	0.571
CI <sup>a</sup>	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
WC (cm) <sup>a</sup>	96(82-105)	79(69-85)	102(93-110)	100(96-107)	<0.001	<0.001	0.755
WHR <sup>a</sup>	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 <sup>*</sup>	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
RDW_CV% <sup>*</sup>	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) <sup>*</sup>	9.8 (8.97-10.53)	9.3 (8.55-9.9)	9.9 (9.2-10.6)	10.35 (9.08-11.03)	.053	0.015	0.277
CCK (pmol/L) <sup>*</sup>	6.79 (4.85-9.62)	5.2 (2.855-7.555)	6.725 (5.055-7.675)	9.67 (7.135-13.705)	0.708	0.129	0.091
OXT (pg/mL) <sup>*</sup>	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	0.071

<sup>a</sup> =P value by Mann-Whitney Test; <sup>b</sup>= P value by Chi-square test, \* = P<sub>value</sub> 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

BMI: body mass Index, CCK: cholecystokinin , CI: conicity index, DBP :diastolic blood pressure, FBG: fasting blood glucose, Hb1Ac: glycated hemoglobin, HDL-C: high density lipoprotein -cholesterol ,LDL-C: low density lipoprotein, MPV: mean platelets volume, OXT: Oxytocin, RDW: red cells distribution, SBP :systolic blood pressure, TC: total cholesterol, TG: triglyceride TG\HDL-c: triglycerides \HDL-C ratio, WC: waist circumference ,WHR: waist circumference –hip circumference ratio.

### 3.2. Demographic and clinical characteristics, biomarkers, adiposity and hematological indices

Table 1 demonstrates the demographic characteristics, findings of basal clinical characteristics, adiposity and hematological indices as well as the levels of molecular biomarkers of the study participants. All participants were Caucasian, the majority of them (61.8%) were females. The median (IQR) age was 41.5(29-52) years and intra-

and inter-group gender distribution had not any statistically significant variations ( $p>0.05$ ). Principally, median BMI was 27.4 (23.77-32.76) kg/m<sup>2</sup>. There were inter-group statistically significant variations ( $p<0.05$ ) in BMI between both MetS and MetS-pre/T2DM groups in comparison to the control group, but there was no significant differences in BMI between diabetic and non-diabetic MetS patients ( $p>0.05$ ). Fasting blood glucose

(mg/dL) and HbA1c (%) were significantly higher ( $p < 0.001$ ) in MetS-pre/T2DM when compared to both normoglycemic control and nondiabetic MetS groups (112(103-118.3), vs. 86(79.75-93.25) and 87(79.5-90) respectively), as well as (5.9 (5.73-6.8) vs. 5.4 (5.2-5.53) and 5.25 (5.1-5.43), respectively).

In perfect alignment with definitive MetS components clustering, the following parameters were significantly higher ( $p < 0.001$ ) in the MetS and MetS-pre/T2DM groups when compared to the lean healthy control group: systolic blood pressure (SBP; mmHg) (135(127.5-141.25) and 140(135-147.5) vs. 120(115-126.25)); diastolic blood pressure (DBP; mmHg) (84(76.5-85.5) and 85(77.5-90) vs. 75(70-80)); triglyceride (TG; mg/dL) (199(156.25-262) and 179.5(127.7-242.5) vs. 72(49.25-94.25)); waist circumference (WC; cm) (102(93-110) and (100(96-107) vs.(79(69-85)). Moreover, low density lipoprotein-cholesterol (LDL-C; mg/dL) levels were significantly higher in the MetS and MetS-pre/T2DM groups when compared to the control group (111.5(84.5-154.98) and 130.5(101.7-174.3) vs. 88(74.25-119);  $p = 0.026$ ,  $p < 0.001$ ). Meanwhile, high density lipoprotein-cholesterol (HDL-C, mg/dL) was significantly lower ( $p < 0.001$ ) in MetS and MetS-pre/T2DM groups vs. lean healthy controls (38(34.5-40) and 38.4(34.6-42) vs. 50(44-70.5)). However, all the above MetS-related components were not substantially different in MetS-pre/T2DM group when compared to those of MetS group. Additionally, total cholesterol (mg/dL) was significantly higher ( $p = 0.025$ ) in MetS group when compared to the control group (207(163.5-230.5), vs. 169 (131.25-209.75). Interestingly, MetS-pre/T2DM group's total cholesterol was not significantly different from either control or MetS groups (Table 1).

Principally, MetS-related conicity index (C-index) and TG/HDL-C ratio (atherogenicity index) were identified as significantly higher ( $p < 0.001$ ) in the MetS and MetS-pre/T2DM groups as compared to the control group (1.15(1.08-1.22) and 1.15(1.06-1.18) vs. 0.97(0.87-1.05)) and (5.105(3.79-6.75) and 4.68(2.16-6.55) vs. 1.31(0.94-1.97)), respectively (Table 1). Moreover, MetS-related waist to hip ratio (WHR) and red blood cell distribution

width (RDW-CV%) were also proven substantially higher in MetS and MetS-pre/T2DM groups vs. control group (0.91(0.88-0.93) and 0.9(0.87-0.92) vs. 0.82(0.75-0.91);  $p < 0.001$ ,  $p = 0.006$ ) and (13.3(12.5-14) and 13.6(12.93-14.6) vs. 13.1(12.2-13.7);  $p < 0.001$ ,  $p = 0.011$ ), respectively (Table 1). The significantly higher median ( $p = 0.015$ ) in mean platelet volume (MPV; fL) was proven for MetS-pre/T2DM group (but not for MetS group;  $p = 0.053$ ) when compared to the control group (10.35(9.08-11.03), vs. 9.3(8.55-9.9) fL). However, all the above MetS-related indices were not ascribed any statistically marked variation in MetS group when compared to MetS-pre/T2DM group (Table 1). Table 1 and Fig. 2 show that CCK plasma levels (pmol/L), interestingly, lacked any statistically significant variations in MetS and MetS-pre/T2DM groups in comparison to healthy controls (9.67 (7.14 – 13.7) and 6.73 (5.06 – 7.68) vs. 5.2 (2.86 – 7.56),  $p > 0.05$  respectively). Comparably, MetS groups, both pre/diabetic and nondiabetic patients, also had not any marked intergroup variation in molecular CCK biomarker concentrations. Conversely, controls' OXT plasma levels (pg/mL) were pronouncedly higher vs. those of MetS and MetS-pre/T2DM groups (4176.6(2407.13-5243.3) vs. both 1975.4(1522.25-3191.15) and 1403(1033.95-2567.3); ( $p = 0.009$ ,  $p = 0.001$ ) respectively). Interestingly, OXT was not described as substantially different in MetS vs. MetS-pre/T2DM ( $p = 0.071$ ; (Table 1 and Fig.3).

### **3.3. Inter-group gender based differences in plasma levels of biomarkers**

Table 2 displays the intergroup gender-based differences in adiposity, hematological indices and both biomarkers. It had been found that both females and males in MetS and MetS pre/T2DM groups had significant inter-group gender-based differences vs. respective control genders in age, BMI, CI, WC, and TG/HDL-C atherogenicity index ( $p < 0.05$ ) but not in either MPV or RDW indices. Surprisingly, only females in MetS and MetS pre/T2DM groups had marked inter-group gender-based variations in WHR vs. respective control females. Obviously, males (but not females in both MetS groups; pre/diabetic and diabetic patients, had markedly higher

CCK (pmol/L) plasma levels vs. control males. Meanwhile, MetS females (but not MetS males) were identified with pronouncedly lower OXT circulating levels vs. control females. It was also observed that both MetS-pre/T2M genders were described with substantially lower

OXT circulating concentrations in comparison to respective control genders. Particularly, no comparable intra-group differences were obtainable for respective genders in pre/diabetic vs. non diabetic MetS groups.

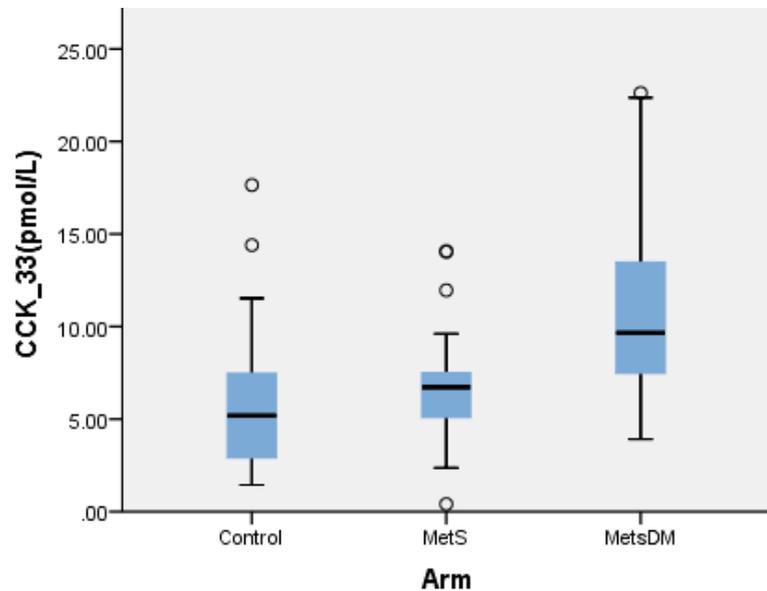


Figure 2: Comparison of circulating levels of CCK in study arms Results are presented as median –IQR (BOXPLOT)

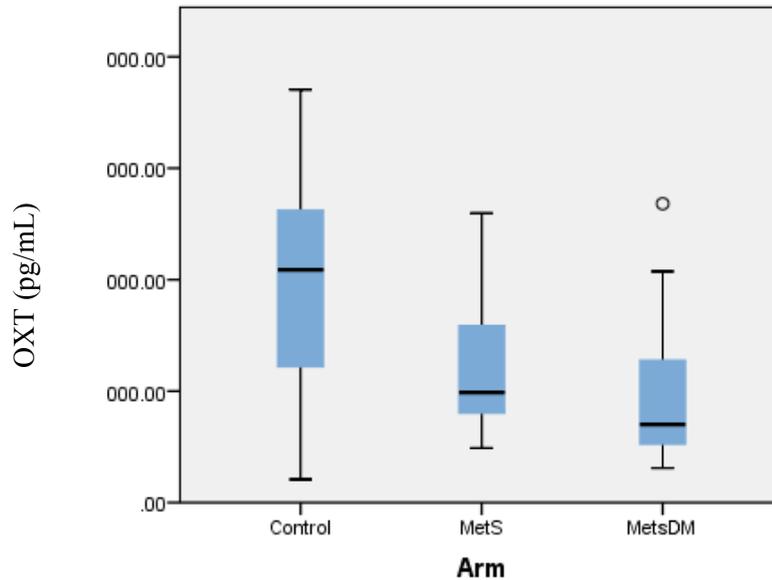


Figure 3: Comparison of circulating levels of OXT in study arms. Results are presented as median –IQR (BOXPLOT)

**Table 2. Intergroup gender-based differences in adiposity markers, hematological indices and plasma levels of CCK and OXT**

Parameters\ biomarkers	Females							Males						
	Total female subjects N=55	Control Group N=22	MetS Group N=19	MetS pre/T2DM Group N=14	P1	P2	P3	Total male subjects N=34	Control Group N=8	MetS Group N=11	MetS pre/T2DM Group N=15	P1	P2	P3
<b>BMI (kg/m<sup>2</sup>)<sup>a</sup></b>	26(22.6-32.8)	21.4 (19.5-24.5)	31.2 (29.4-36)	32.7 (26.2-36.7)	< 0.001	<0.001	0.855	29.7 (24.8-32.7)	22.8 (21.4-24.6)	30.8 (26.7-34.5)	31.4 (28.4-32.9)	0.001	<0.001	0.551
<b>CI<sup>a</sup></b>	1.03(0.95-1.2)	0.89 (.86-1)	1.1(1.03-1.2)	1.07 (1.03-1.2)	<0.001	<0.001	0.229	1.1 (1.09-1.2)	1.06 (.99-1.1)	1.2 (1.1-1.2)	1.2 (1.1-1.2)	0.002	<0.001	0.856
<b>WC(cm)<sup>a</sup></b>	92(80-105)	79.5 (70-90)	102.5 (96.5-114.25)	99 (93.5-107.5)	<0.001	<0.001	0.446	98.5 (82-105)	74.5 (68-82.62)	102(88-106)	101 (96-110)	0.001	<0.001	0.646
<b>WHR<sup>a</sup></b>	0.86(.78-.91)	0.79 (.74-.84)	1.2 (1.03-1.2)	0.87 (.80-.90)	0.001	0.031	0.115	0.91 (0.89-0.95)	0.90 (0.85-0.95)	0.93 (0.91-0.97)	0.90 (0.88-0.96)	0.213	0.43	0.137
<b>TG\HDL-C<sup>*</sup></b>	2.1(1.03-4.5)	1.1 (.79-1.5)	4.4(3-5.5)	2.3 (1.8-5.9)	< 0.001	0.007	0.129	5.1 (2.7-6.6)	2.1 (1.6-2.7)	6.2 (5.1-9.6)	5.2 (4.1-6.9)	0.002	0.015	0.294
<b>RDW (CV%)*</b>	13.3(12.5-14)	13 (12.2-13.7)	13.3 (12.4-13.4)	13.3 (12.5-14.1)	0.694	0.433	0.507	13.3 (12.6-14)	13.1 (11.8-13.3)	13.8 (13-14.5)	13.3 (12.8-14.3)	0.186	0.223	0.923
<b>MPV (fL)*</b>	9.7(9.03-10.5)	9.2 (8.5-9.8)	9.9(9.5-10.6)	9.8 (9.03-10.5)	0.443	0.083	0.115	10.1 (8.9-10.6)	9.3 (8.3-10.5)	9.9 (9.02-10.5)	10.2 (8.9-11.3)	0.952	0.807	0.776
<b>CCK (pmol/L)*</b>	6.8 (4.4-9.9)	5.4 (3.5-8.4)	6.35 (4.5-7.2)	12.9 (8.9-14.6)	0.061	0.892	0.052	7.3 (5-9.5)	3.8 (1.8-6.1)	7.3 (5.5-11.9)	8.2 (6.6-10.3)	0.017	0.018	0.921
<b>OXT (pg/mL)*</b>	2501 (1397.7-3802.3)	3783.5 (2324.9-4820.2)	1975.4 (1439.5-3540.2)	2501 (1397.6-3802.3)	0.026	0.023	0.357	1880.1 (1136.8-4197.4)	5092.3 (4186.9-5605.3)	2030.4 (1529.8-2667.7)	1278.5 (978.8-3869.8)	0.232	0.022	0.068

= P<sub>value</sub> by Mann-Whitney Test

\* = P<sub>value</sub> 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

BMI: body mass Index, CCK: cholecystokinin, CI: conicity index, OXT: Oxytocin, RDW: red cells distribution, TG\HDL-c: triglycerides\

HDL- Cratio, WC: waist circumference ,WHR: waist circumference –hip circumference ratio

### 3.4. Gender-based correlations of metabolic biomarkers, adiposity and haematological indices

Table 3 demonstrates the associations of metabolic biomarkers, obesity and blood parameters in females and males of all study participants. Our study found that anthropometric parameters (BMI, CI, WC and WHR) significantly correlate with each other in females in a positive way, while in males both (BMI and CI) are associated significantly and directly to each other. Moreover, BMI substantially and positively correlates with WC, but there was not any correlation with WHR, as well as there was no significant associations between CI and both WC and WHR. Based on the results of our study, atherogenicity index (TG\HDL-c) significantly and directly correlates with (BMI, CI and WC), but there was not any

correlation with WHR in both females and males. RDW substantially and directly is associated with (BMI, CI and TG\HDL-c) in males but with MPV only in females. However, in females MPV significantly and directly correlates with (BMI, CI and RDW), but this blood parameter had significant association neither with anthropometric parameters nor with atherogenicity index and blood indices .Our study found that CCK had no significant correlations with BMI, CI, WC, WHR, TG\HDL-c, RDW, MPV, or OXT in females, whereas it substantially and directly correlates with BMI, CI and WC but indirectly with OXT in males. OXT is associated substantially but negatively with BMI and WC in both females and males.

Table 3. Gender-based associations of adiposity, blood indices and metabolic biomarkers

Parameter (s)	Correlation	Total females population									Total males population								
		BMI	CI	WC	WHR	TG\HDL	RDW	MPV	CCK	OXT	BMI	CI	WC	WHR	TG\HDL	RDW	MPV	CCK	OXT
BMI (Kg/m <sup>2</sup> )	R	1.000	0.761**	0.711**	0.473**	0.648**	0.186	0.303*	0.066	-0.292*	1.000	0.790**	0.396*	0.127	0.457**	0.399*	0.237	0.374*	-0.379*
	Sig (2-tailed)		<0.001	<0.001	<0.001	<0.001	0.187	0.032	0.634	0.036		<0.001	0.021	0.474	0.007	0.024	0.192	0.032	0.030
CI	R	0.761**	1.000	0.610**	0.608**	0.584**	0.169	0.238	-0.002	-0.252	0.790**	1.000	0.292	0.289	0.495**	0.464**	0.278	0.348*	-0.261
	Sig (2-tailed)	<0.001		<0.001	<0.001	<0.001	0.232	0.096	0.987	0.071	<0.001		0.093	0.097	0.003	0.008	0.123	0.047	0.142
WC(cm)	R	0.711**	0.610**	1.000	0.358**	0.488**	0.229	0.370**	0.052	-0.363**	0.396*	0.292	1.000	0.114	0.448**	-0.019	0.199	0.378*	-
	Sig (2-tailed)	<0.001	<0.001		0.009	<0.001	0.110	0.010	0.716	0.010	0.021	0.093		0.522	0.008	0.919	0.275	0.030	<0.001
WHR	R	0.473**	0.608**	0.358**	1.000	0.263	0.186	0.109	-0.072	-0.271	0.127	0.289	0.114	1.000	0.106	-0.002	-0.178	0.282	-0.064
	Sig (2-tailed)	<0.001	<0.001	0.009		0.052	0.186	0.452	0.604	0.052	0.474	0.097	0.522		0.552	0.990	0.331	0.111	0.723
TG\HDL-C	R	0.648**	0.584**	0.488**	0.263	1.000	0.028	0.254	0.040	-0.212	0.457**	0.495**	0.448**	0.106	1.000	0.379*	0.117	0.209	-0.270
	Sig (2-tailed)	<0.001	<0.001	<0.001	0.052		0.842	0.075	0.776	0.132	0.007	0.003	0.008	0.552		0.032	0.524	0.243	0.129
RDW (CV%)	R	0.186	0.169	0.229	0.186	0.028	1.000	0.429**	0.037	-0.023	0.399*	0.464**	-0.019	-0.002	0.379*	1.000	0.167	0.074	-0.104
	Sig (2-tailed)	0.187	0.232	0.110	0.186	0.842		0.002	0.795	0.874	0.024	0.008	0.919	0.990	0.032		0.360	0.694	0.571
MPV (fL)	R	0.303*	0.238	0.370**	0.109	0.254	0.429**	1.000	-0.009	0.052	0.237	0.278	0.199	-0.178	0.117	0.167	1.000	-0.177	-0.181
	Sig (2-tailed)	0.032	0.096	0.010	0.452	0.075	0.002		0.949	0.726	0.192	0.123	0.275	0.331	0.524	0.360		0.341	0.323
CCK (pmol/L)	R	0.066	-0.002	0.052	-0.072	0.040	0.037	-0.009	1.000	-0.162	0.374*	0.348*	0.378*	0.282	0.209	0.074	-0.177	1.000	-0.414*
	Sig (2-tailed)	0.634	0.987	0.716	0.604	0.776	0.795	0.949		0.252	0.032	0.047	0.030	0.111	0.243	0.694	0.341		0.019
OXT (pg/mL)	R	-0.292*	-0.252	-	-0.271	-0.212	-0.023	0.052	-0.162	1.000	-0.379*	-0.261	-	-0.064	-0.270	-0.104	-0.181	-	1.000
	Sig (2-tailed)	0.036	0.071	0.010	0.052	0.132	0.874	0.726	0.252		0.030	0.142	<0.001	0.723	0.129	0.571	0.323	0.019	

R=Correlation Coefficient

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

BMI: body mass Index, CCK: cholecystokinin, CI: conicity index, HDL-C: high density lipoprotein -cholesterol, LDL-C: low density lipoprotein, MPV: mean platelets volume, OXT: Oxytocin, RDW: red cells distribution, TG: triglyceride TG\HDL-c: triglycerides \HDL-C ratio, WC: waist circumference, WHR: waist circumference -hip circumference ratio.

#### 4. DISCUSSION

Obesity is associated with IR and the MetS contributes to hypertension, high serum cholesterol, low HDL-C and hyperglycemia<sup>(3)</sup>. It is independently associated with CVD risks. Increasing BMI is associated with a risk of serious health consequences in the form of T2DM, coronary heart disease (CHD) and a range of other conditions, including some forms of cancer<sup>(2)</sup>. It had been found that WHR was the best index to make a distinction between individuals who had T2DM. Moreover, WC and BMI are not only the simplest to obtain, but also the most accurate surrogate markers of visceral adiposity in young adults, and are good indicators of IR<sup>(25)</sup>. MPV and RDW were significantly higher among diabetic subjects compared to apparently healthy controls. It had been found that the routine hematological profile checking of patients with T2DM

may help in preventing complications associated with variations in hematological values<sup>(26)</sup>. In addition to the adiposity and hematological indices, we investigated atherogenicity index, which is TG\HDL-c ratio, because it was the single most powerful predictor of extensive coronary heart disease among all the lipid variables examined<sup>(27)</sup>. OXT exerts direct actions on glucose and insulin homeostatic machinery independently of body weight control. The patients who underwent the treatment showed slight improvement in hepatic function, and importantly, OXT yielded all these metabolic benefits but without having the negative side effects on cardiovascular, liver or kidney functions; problems reflected by most anti-obesity drugs marketed recently<sup>(14)</sup>. A more recently developed enzymatically stable, N-terminally modified, CCK analogue, namely (pGlu-Gln)-CCK-8, has been

shown to have an improved pharmacodynamics profile, and to both alleviate and protect against obesity-related diabetes in animal models, with an encouraging safety profile<sup>(28)</sup>. Peripheral CCK administration decreases food intake by reducing meal duration as well as the quantity of the ingested food, while centrally administrated CCK also decreases food intake<sup>(29)</sup>.

#### **4.1. Comparison of our participants' characteristics and clinical parameters to those of Jordanian DM patients**

The diabetic participants' median age was 52 (43.5-55) years. This is lower than the mean age of Jordanian diabetics' 55.5±10.6 years. Median body mass index in our diabetic population was 31.8 (27.5-35.2), which was comparable to that observed among Jordanian diabetics (32.20 ± 5.81 kg/m<sup>2</sup>) reported by Ajlouni *et al.*<sup>(30)</sup>.

#### **4.2. Comparison of clinical characteristics and biomarkers in our study vs. those from other studies**

In a cross-sectional study by AL-Nouaaimi *et al.*<sup>(31)</sup> originally 166 subjects were chosen but 77 subjects, who were MetS-apparently healthy control and 89 patients who were with MetS pre-T2DM groups, participated in this study in order to investigate plasma OXT levels. In our study, a total 89 subjects were assigned into controls, MetS and MetS-pre-T2DM. The case group included 59 patients, who were MetS patients, and who were also non-diabetic or newly diagnosed with either prediabetes or T2DM to detect plasma levels of OXT and CCK. On the other hand, 30 normoglycemic lean individuals were included. In both studies, all subjects in three groups did not receive any antidiabetic treatment including oral hypoglycemic. Comparable to AL-Nouaaimi *et al.*,<sup>(31)</sup> the circulating concentrations of OXT were significantly lower in diabetic metabolic syndrome patients than those non-diabetic metabolic syndrome (2253.71±851.24) vs.(1206.28±507.68) (p<0.001). Unlike our study, the OXT levels in our population of nondiabetic MetS (1975.4 (1522.25-3191.15) were not significantly different from those in MetS pre-T2DM (1403(1033.95-2567.3) (p=0.071).

Rushakoff *et al.*<sup>(32)</sup> had argued that there were no significant discrepancies in CCK levels between healthy (1.2±0.2) and diabetics individuals (1.1 ±0.2) (P=.079) as is the case in our findings; where CCK levels in control (5.2(2.855-7.555)) and MetS pre-T2DM (9.67(7.135-13.705)) groups were marginally different, but statistically this difference was insignificant (Table 1, p>0.05). According to Foschi *et al.*,<sup>(33)</sup> the CCK levels in controls (0.26 ± 0.66) were not substantially different from MetS patients (0.45 ± 0.51, p>0.05). Similar to the findings of Foschi *et al.*,<sup>(33)</sup> our findings illustrate that CCK levels lacked statistically significant deviations between healthy (5.2(2.855-7.555)) and MetS subject (6.725(5.055-7.675), as shown in Table 1, p=0.708). Notably, the preferable acute beneficial metabolic and gastrointestinal (GI) hormone responses (CCK inclusive) in MetS adults based on therapeutic life style modifications have been founded on the pre-interventional gut hormones dysregularities<sup>(34)</sup>. Thus, principally clinical relevance of our findings (due to sample size limitations) could not be soundly appraised in our cross sectional study design.

Furthermore, it has been found that CCK and estradiol positively correlated to each other; therefore, estradiol deficiency in postmenopausal women could contribute to altered sensitivity to CCK. In addition, the plasma concentration of estradiol in males is 2-3 ng/dL and its production rate in blood is 25-40 micrograms/24 h; both of these values are significantly higher than in postmenopausal women and this may explain why the levels in men were higher than those in women<sup>(35-36)</sup>.

Although in Al-Rawashdeh *et al.*<sup>(37)</sup> the sample sizes per nondiabetic and pre/diabetic MetS study arms were immeasurably greater, unlike our current study, the healthy lean normoglycemic controls were lacking along with the hematological, adiposity and atherogenicity indices [CI,TG\HDL-c ratio, MPV,and RDW] in the MetS clinical significance and impact. Taken together, our present study reflects on the cross sectional correlates of both Oxytocin and cholecystokinin with atherogenicity and adiposity indices of metabolic syndrome (nondiabetic, prediabetic and diabetic) patients.

#### 4.3. Study limitations

This is a cross-sectional study which limits the interpretation and speculations of the results in order to obtain a cause-effect relationship between the biomarkers and obesity as well as diabetes. The inclusion of a diabetic group on medication could have provided us with further evidence of the effect of diabetes duration. Additional clues for whether a good glycemic control could have had any influence on the circulating biomarkers may be inferred.

#### 4.4. CONCLUSIONS

WC was substantially higher in both MetS and MetS Pre/T2DM groups' patients compared to healthy-lean controls. Both FPG and Hb1Ac % were significantly higher in MetS Pre/T2DM groups' patients than in both healthy controls and nondiabetic MetS subjects. Interestingly, circulating levels of OXT were significantly lower in both nondiabetic MetS and MetS Pre/T2DM groups' participants when compared to healthy controls. Basically, there was no significant difference in OXT levels between nondiabetic MetS and MetS-Pre/T2DM groups' patients. Furthermore, there were no inter-group

significant differences in CCK levels. OXT had intergroup gender-based differences for both males and females, while CCK had inter group gender-based differences for males but not for females.

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#### COMPLIANCE WITH THE ETHICAL STANDARDS

This study has been conducted in accordance with 1964 Helsinki declaration. All procedures performed in this study with human participants were in accordance with the ethical standards of the IRB (Institutional Review Board) Committees affiliated with the National Center for Diabetes, Endocrinology, and Genetics (NCDEG) (101675/9/SM) and the Scientific Research Committee of the School of Pharmacy as well as the Deanship of Academic Research and Quality Assurance - (no.1370 /2016) the University of Jordan.

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## ترابط الأوكسيتوسين والكوليبيستوكينين مع مؤثرات متلازمة اضطراب الأيض ومؤشرات الشحوم الأيضية

طيبة فارس الأعظمي<sup>1,2</sup>، فيوليت كسابري<sup>1\*</sup>، رندا نفاع<sup>2</sup>، أمل العكور<sup>1</sup>، دانا الحياصات<sup>3</sup>، ياسر البستنجي<sup>1,4</sup>

<sup>1</sup> كلية الصيدلة، الجامعة الأردنية، شارع الملكة رانيا، عمان 11942، الأردن

<sup>2</sup> كلية الطب، الجامعة الأردنية، شارع الملكة رانيا، عمان 11942، الأردن

<sup>3</sup> المركز الوطني للسكري والغدد الصماء والأمراض الوراثية، شارع الملكة رانيا، عمان 13165، الأردن

<sup>4</sup> مركز حمدي منكو للأبحاث، الجامعة الأردنية، عمان 11942، الأردن

\* كلية الصيدلة، الجامعة الأردنية، شارع الملكة رانيا، عمان 11942، الأردن

### ملخص

الأهداف: هدفت هذه الدراسة إلى تحقيق الترابط بين مستوى بلازما لكل من الأوكسيتوسين والكوليبيستوكينين وكذلك مؤشر سمنة الخصر، ومحيط الخصر، نسبة محيط الخصر إلى محيط الورك، ومؤشر تصلب الشرايين (نسبة الدهون الثلاثية م الثلاثية إلى البروتين الدهني العالي الكثافة (1)، وقياس توزيع كريات الدم الحمراء ومعدل حجم الصفائح الدموية، حيث يتقاسمون الأدوار الحاسمة في تطور وتقدم متلازمة الاضطراب الأيضي، ومقاومة الانسولين وداء السكري من النوع الثاني. الطرق: في دراسة مسحية، 30 شخصاً لديهم مستوى السكر والدهون الطبيعي (المجموعة 1)، 30 مريضاً مع متلازمة الاضطراب الأيضي (المجموعة 2)، 29 مريضاً مع متلازمة الاضطراب الأيضي مع ما قبل السكر / السكري النوع 2 (المجموعة 3)، حيث انهم كانوا متطابقين من حيث مؤشر كتلة الجسم والجنس والعمر. وقد تم قياس الكوليبيستوكينين في البلازما عن طريق الفحوصات اللونية الأوتوميية. وقد تم فحص الارتباط بين هذه المؤشرات الحيوية الأيضية، وكذلك مؤشرات السمنة والمؤشرات الدموية للمشاركين في الدراسة.

النتائج: إن متوسط مستويات الأوكسيتوسين في المجموعة 1 كانت أعلى مقارنة بمجموعة المرضى الذين يعانون من متلازمة الاضطراب الأيضي فقط أو مع المرضى الذين يعانون من متلازمة الاضطراب الأيضي بالإضافة إلى مرحلة ما قبل السكري أو السكري من النوع الثاني ( $p=0.009$ ;  $p=0.001$ ) على التوالي. مع ذلك ومن المثير للاهتمام فإن مستويات الكوليبيستوكينين ( $\text{pmol/L}$ )؛ تفتقر إلى اختلافات ذات دلالة احصائية في مجموعتي الاضطراب الأيضي والمصابون بداء السكري مقارنة مع مجموعة الاصحاء  $p>0.05$  تباعاً.

نسبياً لم يكن هناك اختلاف واضح بين مجموعة رقم (2) ومجموعة رقم (3) في تراكيز الكوليبيستوكينين. بالإضافة إلى انه في مجموعتي (2) و(3) كان فيها (مؤشر تصلب الشرايين، ومؤشر سمنة الخصر وقياس توزيع كريات الدم الحمراء، ومحيط الخصر، ونسبة محيط الخصر إلى الورك) أعلى بكثير ( $p>0.05$ ) مقارنة مع مجموعة رقم (1). من المثير للاهتمام ان معدل حجم الصفائح الدموية في مجموعة رقم (3) كان أعلى بشكل جوهري ( $p=0.015$ ) مقارنة بمجموعة رقم (1) مع ذلك فإن المؤشرات المتعلقة بمتلازمة الاضطراب الأيضي لم تسجل أي اختلاف احصائي ملموس بين مجموعتي مرضى الاضطراب الأيضي ومرضى السكري.

الخلاصة: أن مستويات الأوكسيتوسين كانت منخفضة بشكل ملحوظ لدى المرضى الذين يعانون من متلازمة الاضطراب الأيضي فقط أو مع المرضى الذين يعانون من متلازمة الاضطراب الأيضي بالإضافة إلى مرحلة ما قبل السكري أو السكري من النوع الثاني مقارنة مع الأشخاص الاصحاء على خلاف الكوليبيستوكينين.

الكلمات الدالة: كوليبيستوكينين، الأوكسيتوسين، مؤشرات الدم والسمنة.

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