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A New Biochemical Trying to Evaluate Levels of Oxytocin and Serotonin in the Serum of Patients Undergoing to Different Strategies for Reducing Weight

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Abstract

Every day, life requires levels of high of physical activity and food, the tendency genetic prefer to store excess calories in order to help body for staying at the level of alive, so an overweight is mean increase the body weight compared with the level of weight acceptable to the normal. Its belief that obesity is a result for losing of ability to correct habits of eating. Obesity is not a single disease, there are 300 different genes were linked to obesity, in addition to several environmental factors could be associate to obesity happening, while most considerations common indicted to the fact that obesity process is a result of an interaction of environmental factors with the genetic predisposition lead to fat accumulation and increased in the adipose tissues.Biochemically, serotonin is synthesized in the intestine enterochromaffin cells, in addition to central and peripheral neuron cells. Serotonin is a neurotransmitter, it contributes to the feelings well-being and happiness,firstly it found in the GIT, especially intestinal mucosa, and platelets, while high concentration of serotonin were recorded in the CNSand pineal body for animals as well as the human. Oxytocin is producing a first in SON and PVN of the hypothalamus, secreted by the posterior pituitary, it has strong contraction effects on the smooth muscle such as in the uterus and breast.

Subjects:47patients (33.28 ±7.424 years with age range 34 years) and 24 healthy individuals (25.96 ± 3.983 years with age range 13 years) were enrolled in the present study. Patients with BMI more than 30 Kg/m^2 (45.179 ± 9.09 Kg/m^2, and 38.7 Kg/m^2 as BMI range); haven't diabetes mellitus, they aren't subjected to obesity surgical operation before. Control group might at approximate age range with the patients group, with similar food style. Average BMI of no smoking, no alcohol drinking healthy group was 18.5 Kg/m^2 (22.829 ± 0.752 Kg/m^2).

Results: A significant decrease ($p = 0.000$) of serum serotonin levels wasrecorded in obese patients group when compared with those of control individuals group.In contrast to basic comparison between the major study groups, no significant differences in the serotonin levels were observed when males and females subgroups were compared together. Negatively significant correlation ($r = - 0.850$ at $p < 0.05$) was observed for serotonin concentrations in the sera of obese patients group with the BMI levels, while no such correlation was observed when serum serotonin levels were correlated to the levels of BMI in the control group. Although a decrease in the mean of oxytocin concentrations which noted in the sera samples of obese subjects was relatively moderate, but good significant variations ($p < 0.05$) were observed at compare the levels of serum oxytocin of obese patients group with the corresponding persons in the control group. Non-significant variations were observed when females and males subgroups were compared together ($p = 0.820$ and $p = 0.350$ for the obese patients and healthy individuals subgroups, respectively). In the obese patients group, respect negative significant differences ($r = - 77.091$ % at $p < 0.005$) were found at the levels of serum oxytocin correlated to their BMI levels illustrated. On the other hand; no significant correlation ($r = - 22.293$ % at $p < 0.005$) recorded in the levels of serum oxytocin to BMI levels in the healthy individuals group.According to the results 83.839 % of patients (a significant positive correlation at $p < 0.005$) showed a decrease in the serotonin and oxytocin levels in serum of obese patients group; simultaneously. Same result, but at the significance level of less (57.497 % at $p < 0.05$), was recorded when the levels of serotonin in sera samples of controls group were correlated to the levels of oxytocin.

Conclusion: Serotonin and oxytocin levels are affected during the overweight gain; and they correlated directly to BMI.Decrease of obese oxytocin concentrations were more clear at obese male comparison to skinny males, although it was decreased at female and male patients.

Key Words: ***Oxytocin, Serotonin, Obese, Surgical Operation, Bypass, Sleeve and Balloon.***

INTRODUCTION

Obesity is a disorder in the regulation of body weight, diagnosed by gathering the increase of the body fat. Every day, life requires levels of high physical activity and food, the genetic tendency prefers to store excess calories in order to help body for staying at the level of alive[1], as such an overweight means increasing the body weight compared with the level of weight accepted in the normal[2]. **BMI** is the most common way for weight measurement and expression, it is the ratio of the body weight (**Kg**) to the square height (**m^2**)[3]. The range of 18.5-24.9 (Kg/m^2) of BMI is the healthy value, while individuals with BMI 25 – 29.9 (Kg/m^2) are considered overweighed, but persons with 30(Kg/m^2) BMI or more are considered obese; at last, most of 40 (Kg/m^2) are called extremely obese[1].It is believed that obesity is a result for losing of ability to correct habits of eating[4]. Obesity is not a single disease, there are 300 different genes that are linked to obesity, in addition to several environmental factors that could be associatedwith obesitycases[5]. Most considerations are commonly indicted to the fact that obesity process is a result of an interaction of environmental factors with the genetic predisposition that lead to fat accumulation and increase in the adipose tissues[6].

Biochemically, **serotonin** or 5-Hydroxytryptamine (5-HT) is a vasoconstrictor molecule derived form mono amino acid "**Tryptophan**", synthesized in the intestine enterochromaffin cells, in addition to central and peripheral neuron cells[7,8]. Serotonin is a neurotransmitter; it contributes to the feelings of well-being and happiness. Firstly, it is found in the gastrointestinal tract (GIT), especially intestinal mucosa, and platelets, while high concentration of serotonin is recorded in the central nervous system (CNS) and pineal body for animals as well as the human[7].Serotonin has been associated with a group of different behaviors, such as feeding, social behavioral, aggression, suicide concern; moreover, serotonin has been associated with the motor system functions, sleep-awaken cycle and respiratory stability.Finally, it is found in the body weight organization system[8].

Oxytocin is a nonapeptide, containing head (ring part) involved six amino acids with disulfide bond and remained amino acids three formed the tail[9].Oxytocin is produced a first in the supraopticneurous (SON) and para ventricular nuclei (PVN) of the hypothalamus[10]. Oxytocin is secreted by the posterior pituitary, it has strong contraction effects on the smooth muscle such as in the uterus and breast. Oxytocin described, firstly, as a female reproductive hormone with the critical actions in the parturition and lactation[11], as well as metabolism regulation, immune system and to the central nervous system functions such as social memory and attachment, aggression, trust, sexual behavior, learning ability, anxiety, feeding behavior and pain cognition in both sexes[12], as well as in the regulation of cardiovascular function[13].

SUBJECTS AND METHODS

During the period from the beginning of July 2015 to the end of February 2016, 47patients (**33.28 ±7.424 years with age range 34 years**) and 24 healthy individuals (**25.96 ± 3.983 years with age range 13 years**) were enrolled in the present study.Patients with BMI more than 30 Kg/m^2 (**45.179 ± 9.09 Kg/m^2**, and **38.7 Kg/m^2 as BMI range**); haven't diabetes mellitus, they aren't subjected to obesity surgical operation before. In order to treat an excess of their body weight or health problems, the present study patients were underwent to the neumours treatment kinds (surgically or non-surgical operations). The patients' group is classified into three subgroups **according to the type of treatment**; **firstly 3** patients were treated with bypass surgery, **the second subgroup** that included **22** patients,is underwent to sleeve surgery, while **the last subgroup**that included **22**patients,is treated by balloon strategic opinion.Selection of healthy individuals as a control group is based upon several criteria included: an absence of major medical or surgical illness in the previous 5 years, no hospital admissions, no current medication, and a subjective perception of good health as determined by health questionnaire. More than, control group might at approximate age range with the patients group, with similar food style. Average BMI of no smoking, no alcohol drinking healthy group was 18.5 Kg/m^2 (**22.829 ± 0.752 Kg/m^2**). Total information of study groups data was shown in the **Table 1.**

The patients group consisted of 32 (68%) female and15 (32%) male, while controls group consisted of 8 (33%) female and 16 (67%) male.Bypass surgical operation patients group included 3 female only, while sleeve surgical operation patients group were included 15 females and 7 males, finally the group of patients who treated with balloon strategic consisted of 14 females and 8 males.

At the morning with fasting period more than eight hours;5 ml of venous blood samples were collected from 71 from the study groups' individuals, 47 obese patients (BMI **45.179 ± 9.09 Kg/m^2**, and age **33.28 ± 7.424 years**) as a problem group, while healthy individuals (BMI **22.829 ± 0.752 Kg/m^2**, and age **25.96 ± 3.983 years**) as a control group. Sera of patient samples were collected from many private hospitals in the Najaf City, Iraq. The selection of the study cases was based on the clinical diagnosis and the opinion of specialist doctors who identified the best type of treatment for the study cases. Levels of serum Serotonin and Oxytocin were determined byCompetitive ELISAmethod.

The statistical analysis was done using the Statistical Package for the Social Science (SPSS) software for windows, Version 19.0. The results were expressed as mean ± standard deviation (**Mean ± S.D)**. The two study groups data were analyzed with **Student's independent *t*-test**. One way analysis of variance (**ANOVA**) was used to compare parameters in different studied subgroups. **Pearson's correlation** was applied to determined the relations among the laboratory parameters of the present study, significance was determined regression. *p-values* less than 5% ($p < 0.05$) were considered as statistically significant.

RESULTS AND DISCUSSION

Serotonin and oxytocin are two neuromodulators with specific anatomical links; they are important for the regulation and expression of several behaviors such as human affects and socialization. Pharmacologically, several studies indicate a functional interaction between the serotonergic and oxytocinergic systems, both systems have been implicated in the control of stress, anxiety, and social cooperation[14-16].

Serotonin is organized by two independent systems, the first in the central nervous system and the other in the periphery, the blood-brain barrier hinders the passage of peripheral serotonin into central nervous system. Only 2% of the body's serotonin is central nervous system stored. Neural serotonin is supposed to modulate numerous sensory, motor and behavioral processes; moreover, it is involved in the control of feeding behavior and obesity, Previously, it has reported that neural serotonin has a suppressive effect on food intake and tends to decrease body weight gain[17]. On the other hand, peripheral serotonin has not been the subject of such intense object, particularly with respect to body fat and lipid metabolism, even though approximately 98% of the body's serotonin exists in the periphery.

Levels of serum serotonin concentration were measured in the two study groups; obese patients as well as healthy individuals. **Table 2** shows a significant decrease (**p = 0.000**) of serum serotonin levels in obese patients group when compared with those of control individuals group.

This result agreed with numerous researches focused on evaluation of serotonin and / or its mediators levels in the samples of obese subjects comparison to normal weight individuals[18,19].

Decreasing of serotonin levels in serum of obese humans may be explained through a several assumptions, and they are probable combined together in serotonin decreasing : **Supplementation and Conversion of Tryptophan:[20], Reduced of The Serotonin Transporter (SERT)[18,21], Inflammatory, Adipokines, Cytokines, and hormones Network[18,22].**

Table 1: Age and BMI Details In The Patients and Controls Groups

Groups (n)	*Age (year)*			*BMI (Kg/m^2)*		
	Mean ± S.D.	**Min. – Max.**	***Range***	***Mean ± S.D.***	***Min. – Max.***	***Range***
Patients 47	**33.28 ±7.424**	**14 – 48**	**34**	**45.179 ± 9.09**	**30 – 68.7**	**38.7**
Healthy 24	**25.96 ± 3.983**	**22 – 35**	**13**	**22.829 ± 0.752**	**21.5 – 24.4**	**2.9**

Table 2:Levels of Serotonin Concentration (ng / ml) In Sera of Obese Patients and Controls Subjects (Mean ± S.D.)

Subjects (n)	*Serotonin Concentration (ng / ml) Mean ± S.D.*	*Min.-Max.*	*Range*	*p*
Obese 47	**0.615 ± 0.196**	**0.333 - 1.387**	**1.054**	***0.000***
Control 24	**0.876 ± 0.171**	**0.581 - 1.224**	**0.643**	

Table 3: Comparison of Serotonin Levels in Male and Female of Patients and Controls Individuals

Subjects (n)	*Gender (n)*	*Serotonin Concentration (ng / ml) Mean± S.D.*	*Min.-Max.*	*Range*	*p*
Obese 47	Female 31	0.597 ±0.174	0.333-1.218	0.885	*0.317 For 1vs2*
	Male 16	0.650 ± 0.234	0.381-1.387	1.006	*0.159 For 3vs4*
Control 24	Female 8	0.952 ± 0.199	0.693-1.224	0.531	*0.000 For 1vs3*
	Male 16	0.837 ± 0.146	0.581-1.104	0.523	*0.007 For 2vs4*

1: Female Patients, 2:Male Patients, 3: Healthy Females, and 4:Healthy Males. The Mean Difference is Significant at 0.05 Level

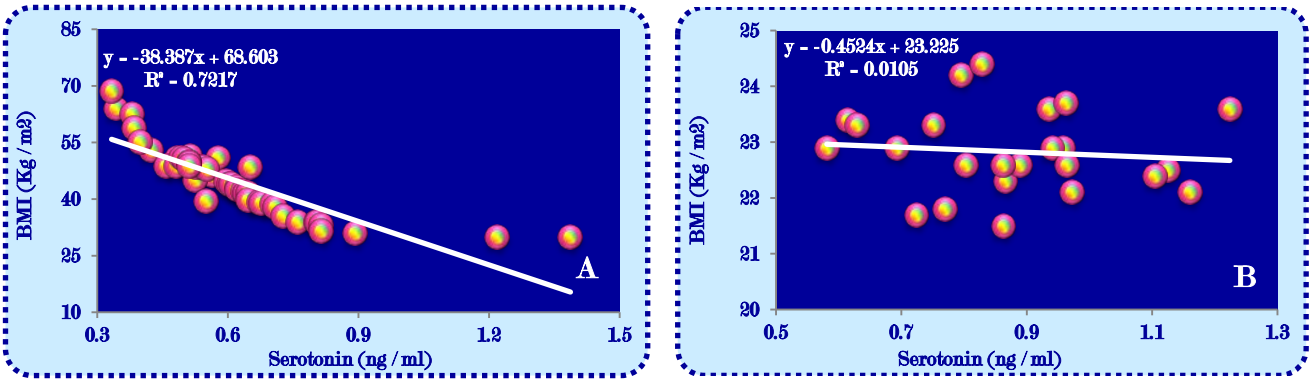

Fig. 1:Correlation of BMIand Serum Serotonin Concentrations in (A):Obese Individuals and (B): Controls

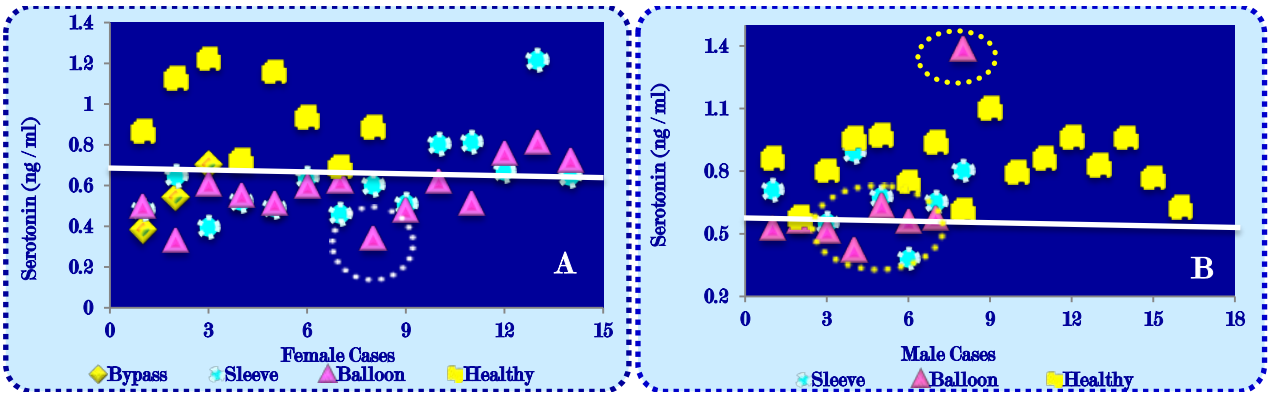

Fig. 2:Gender Differences of Serum Serotonin Levels in obese Patients According to the Type of Treatment Strategies

In contrast to basic comparison between the major study groups, no significant differences in the serotonin levels were observed when males and females subgroups were compared together. **Table 3** recorded similar results when the two healthy subgroups (males and females) were compared.

The present study results agreed with Hodge´s study and other[19,23,24]. In the purpose of study the effect of the BMI in changes of serum serotonin concentrations, linear regression analysis (Pearson's correlation) was used to analyze the results.**Negatively** significantcorrelation **(r = - 0.850** at **p < 0.05)** was observed for serotonin concentrations in the sera of obese patients group with the BMI levels, as recorded in **Figure 1(A)**, while no such correlation was observed when serum serotonin levels were correlated to the levels of BMI in the control group (**Figure 1(B)**).These findings agreed with many studies[17,23,24], on the side, the results of current study appear contradictory to findings of Wurtman study[25].

According to the type of medical treatment to reduce the weight, obese patients were classified into **three subgroups**, including: treatment through**Gastric Bypass** and **SleeveOperations*(theywere done surgically or laparoscopy)***, and finally treatment by **Balloon(*this strategy was done by laparoscopy).***

Novelty of the current work backs to the detailed comparison of the serotonin levels and corresponding BMI at different subgroups in the various techniques used to reduce weight.

Figure 2 (A)demonstrates the distribution of sera serotonin levels in the female study cases (female patients with numerous strategies to reduce of weight in addition to healthy females). Generally, serum serotonin of healthy females is found to be higher than their corresponding females in the patients subgroup (**p < 0.005**), when; except five female patients (3 of them bowed to sleeve treatment "with BMI ranged between **31.4-39 Kg/m^2**" and 2 of them bowed to balloon treatment "with **30 Kg/m^2** BMI"), the 5 females were younger than other patients. The lowest serotonin concentration in sera of healthy females was noted in the **29** years old and **23.6 Kg/m^2** BMI.

In the present work, serotonin levels in the male patient cases were variant to those of healthy individuals **but** with less significant (**p < 0.05**) than these results which recorded in the females subgroup. **Figure 2 (B)**illustrates the relative closeness in the serotonin levels in the different male obese patients and healthy individuals, especially, male patients whose underwent to sleeve of stomach strategy. High BMI male patients who suffered from cardio vascular diseases (CVD) complications and bowed to balloon strategy in order to reduce them over weight; they illustrate the lowest serotonin levels. Isolated case was monitored in the youngest male patient (25 years old), with **33Kg/m^2**as BMI, he illustrate high serotonin level, as shown in the **Figure 2 (B)**.

Levels of Oxytocin Concentration In Sera of Obese Patients and Healthy Individuals:The well-known role of oxytocin in labor and lactation did not draw attention away from a wide range of central and peripheral effects[26]. The central action of oxytocin includes numerous behavioral effects "social and non social behaviors"[27-29] and an effect on memory, also it plays a role in the regulation of food intake then, enhancement of the effectiveness of peripheral satiety signals[30,31]. With the beginning of the present decade, several studies revealed the weight reducing action of oxytocin treatment due to oxytocin induced anorexia with a positive effect on glucose tolerance and insulin sensitivity[32,33].

Although a decrease in the mean of oxytocin concentrations which is noted in the sera samples of obese subjects was relatively moderate, **but** good significant variations **(p < 0.05)** were observed, when compared to the levels of serum oxytocin of obese patients group with the corresponding persons in the control group, as shown in the **Table 4**.

Compared to the recent research studies, which are applied on the obese rats[23] and the present work, current study documented a clear hypooxytocinaemia, when; more than three quarters of the obese patients revealed a deficiency in the oxytocin concentrations **adverse** only 40% of obese rats that illustrated the same results in correlation to their corresponding BMI. No significant variations were observed when females and males subgroups were compared together (**p = 0.820** and **p = 0.350**for the obese patients and healthy individuals subgroups, respectively), as shown in **Table 5.**

The present results disagreed with Stock study[34], which reported that the plasma oxytocin levels were fourfold higher in obese individuals compared with the normal weigh persons regardless gender. In the obese patients group, respect negative significant differences (**r = - 77.091 %** at **p < 0.005**) were found at the levels of serum oxytocin correlated to their BMI levels, as **Figure 3 (A)** illustrated. On the other hand, no significant correlation (**r = - 22.293 % at p < 0.005**) was recorded in the levels of serum oxytocin to BMI levels in the healthy individuals group (**Figure 3 (B)**).

Table 4:Levels of Oxytocin Concentration In Sera of Obese Patients and Controls Subjects (Mean ± S.D.)

Subjects (n)	*Oxytocin Concentration(pg / ml) Mean ± S.D.*	*Min.-Max.*	*Range*	*p*
Obese 47	**0.925 ± 0.282**	**0.393 - 1.382**	**0.989**	***0.020***
Control 24	**1.080 ± 0.206**	**0.612 - 1.439**	**0.827**	

Table 5: Comparison of Oxytocin Levels in Male and Female of Patients and Controls Individuals

Subjects (n)	*Gender (n)*	*Oxytocin Concentration(pg / ml) Mean± S.D.*	*Min.-Max.*	*Range*	*p*
Obese 47	**Female 31**	**0.931 ± 0.299**	**0.393-1.382**	**0.989**	***0.820 For 1vs2***
	Male 18	**0.912 ± 0.252**	**0.521-1.272**	**0.751**	***0.091 For 3vs4***
Control 24	**Female 8**	**1.151 ± 0.199**	**0.924-1.313**	**0.389**	***0.011 For 1vs3***
	Male 16	**1.044 ± 0.206**	**0.612-1.439**	**0.827**	***0.000 For 2vs4***

1: Female Patients, 2:Male Patients, 3: Healthy Females, and 4:Healthy Males. The Mean Difference is Significant at 0.05 Level

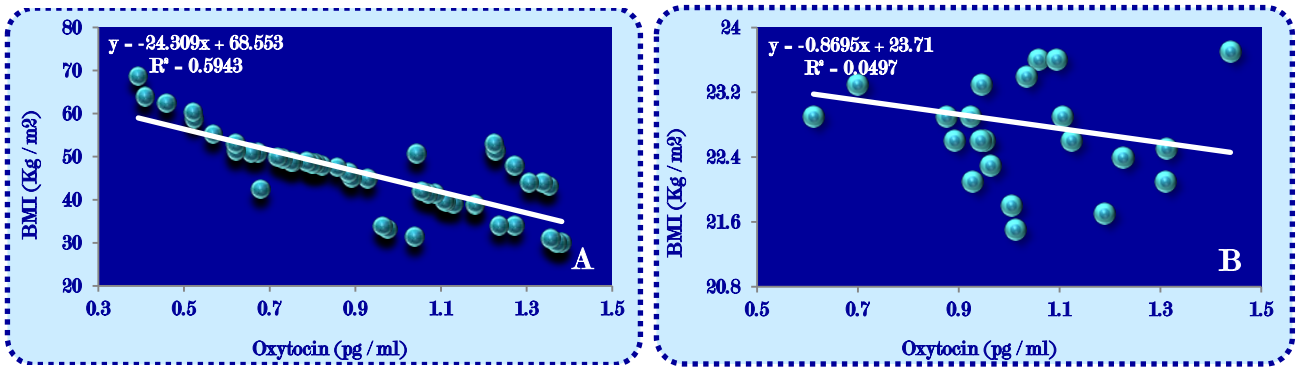

Fig. 3:Correlation of Body Mass Index (BMI) and Serum Oxytocin in (A): Patients and (B): Healthy

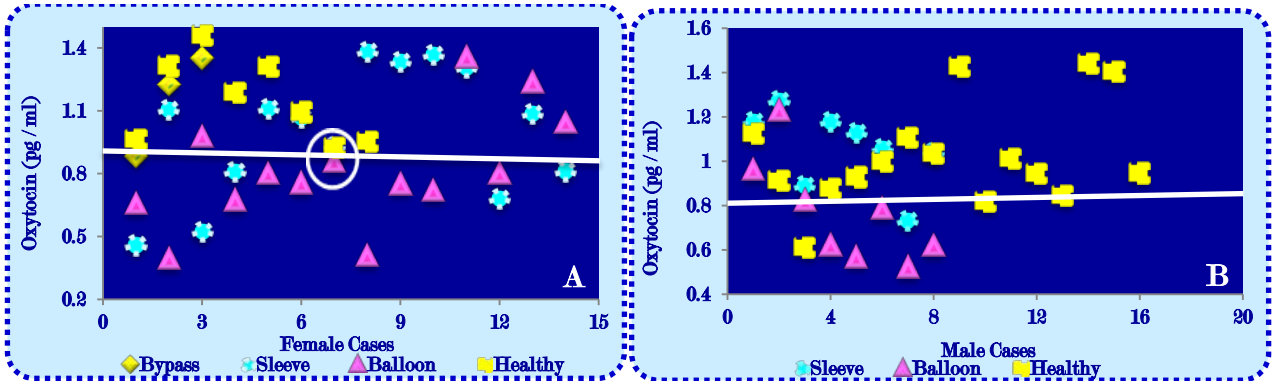

Fig. 4:Gender Differences of Serum Oxytocin Levels in obese Patients According to the Type of Treatment Strategies

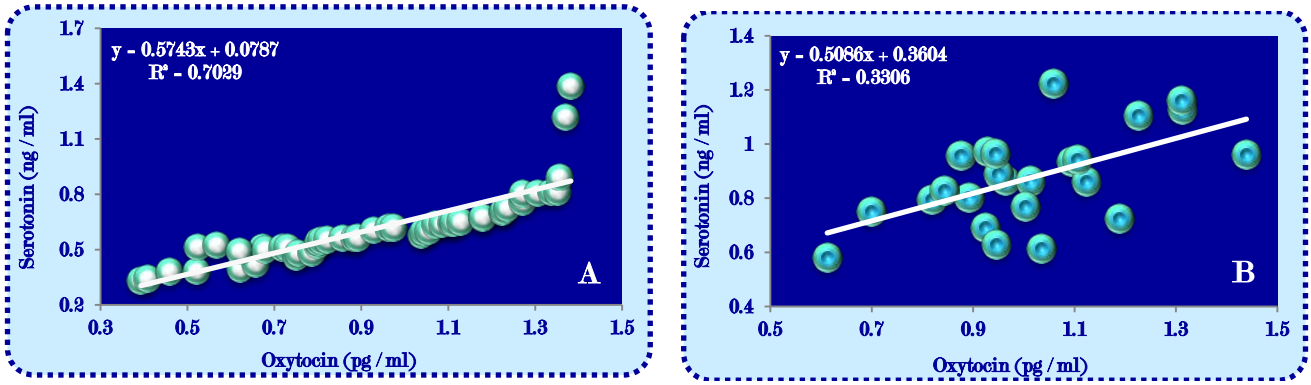

Fig. 5:Correlation Of Serotonin to Oxytocin Concentrations In Sera Samples Of (A):Obese Persons and (B): Normal Controls

Comparison between subgroups of females (obese patients to control subjects) illustrated a statistically significant (**p = 0.038**) decrease in the oxytocin concentrations at the patient females subgroup comparison to those in healthy females. On the other hand, male (obese patients to control subjects) subgroups failed to find statistical differences in the levels of oxytocin. The last finding of the study agreed with Coiro study[35], that illustrated both of obese and normal weight men display similar basal oxytocin levels.

Figure 4 (A) and **(B)** illustrate distribution of oxytocin levels based on the techniques used in the medical weight loss for female and male subgroups, respectively.

Female patients who bowed to balloon technique to reduce the overweight, **especially**; were recorded to be the lowest oxytocin levels among female obese patients, in a manner contrary, it is found that oxytocin levels in the serum of women who underwent other strategies to reduce weight were comparable to what has been recorded in the serum of women control group.

Although the cutoff value (the lowest oxytocin concentration in the healthy individuals sera) of oxytocin (**0.819 pg / ml**) for male was less than what it recorded in the female subgroup (**0.924 pg / ml)**, similar results were observed in the male patients subgroup. These differences in the cutoff values could be attributed to the fact that oxytocin and oxytocin receptors expression is usually higher in females[36], in addition to that, oxytocin and oxytocin receptors distributions in the brains of male and female were different[37].

Clarification the effect of BMI in the selection of the suitable techniques used to body weight reducing, and correlated that to the oxytocin levels, are not showed in previous studies, nor human neither animals.

Oxytocin is produced in the hypothalamus by two types of neurons: magnocellular and parvocellular[31], physiologically, levels of oxytocin depend on its synthesis, receptor mediated internalization and degradation by oxytocinase "**EC 3.4.11.3**". Oxytocinase is a cystinyl amino peptidase enzyme, that inactivates oxytocin via hydrolysis of the peptide bonds between csystein and tyrosine[38]. Oxytocin receptors spread in most of the body tissues, particularly brain, liver, kidney, and fatty tissues, in addition to the smooth tissues.

Several studies followed non social oxytocin action as a regulator of food intake and animal body weight recontrol, these studies showed: at oxytocin and /or oxytocin receptors decrease, that lead to lack of oxytocin action simultaneous by the development of obesity and impaired glucose tolerance[39]. Other study illustrated the peripherally administered of oxytocin at a low dose is inefficient at inhibiting food intake and stimulates adipogenesis *in vivo* without affecting adipose tissue mass[40]. Recent study documented that hypothalamic oxytocin gene expression was not altered by the obese phenotype, while; an elevation of liver and adipose tissue oxytocinase activity was noticed in the obese rats.

Humanly, the beneficial effects of oxytocin treatment, such as weight loss, have been well documented recently[26,41,42]. These observations imply a partial role of oxytocin in the development of obesity.Reduction of the serum oxytocin of the obese subjects in the current work, might explain as a reflex to the arise of oxytocinase activity synchronizlly to the elevation in the BMI.

The Relationship Between Serum Serotonin and Oxytocin Concentrations in The Obese Patients and Control Individuals Groups:The main objective of the present study was to assess the possible existence of interactions between the serotonin and the oxytocin levels at humans suffered an excess in the weight in addition to persons could be describe as an ideally human weight.

For this purpose, the selected two peripheral markers were evaluated in the sera samples of the two study groups. The correlation of serum serotonin to oxytocin in obese patients in addition to healthy individuals was evaluated using the linear regression analysis.

According to the results in **Figure 5 (A)**, **83.839 %** of patients (a significant positive correlation at **$p < 0.005$**) showed a decrease in the serotonin and oxytocin levels in serum of obese patients group;simultaneously. Same result, **but at the significance level of less** (**57.497 %** at **$p < 0.05$**), was recorded when the levels of serotonin in sera samples of controls group were correlated to the levels of oxytocin, as revealed in **Figure 5 (B)**, that is to say, the lowest of the serotonin values similarity the lowest oxytocin values, and vice versa.

These findings may be considered as in agreement with different data showing that serotonin and oxytocin systems interact at different levels, both anatomically[43,44]and functionally[45]. The current study coincided, especially with previous medical observation that was recorded the fact, the systemic treatment of fenfluramine or p-chloroamphetamine (serotonin agonists), increases oxytocin concentrations and expression in oxytocin neurons[46]. In addition, Plasma oxytocin levels have been observed to increase also in healthy subjects following the administration of fenfluramine[47].

Emiliano and his colleagues[48] have highlighted the links between the oxytocin system and SERT in non-human primates, on the other side, Yoshida team [49] published report was indicated that oxytocin may regulate the serotonin release via activation of oxytocin receptors in serotonergic neurons of the median raphe nuclei in mice. Montag study[50] illustrated a strong interaction effect between the SERT-linked-promoter polymorphism and a variant of the oxytocin gene on the personality dimension of fear and sadness and on negative emotionality, by using a principal component analysis. The study of Marazziti team which published at 2013 have been adverted to the really relationship between platelet SERT as an indicator to the peripheral concentration of serotonin and plasma oxytocin using an advance chemical and mathematical experimentally tests[45].

Supplementary, previous work[49] revealed that long time treatment of SSRIs drugs like citalopram and fluvoxamine, increased oxytocin levels[51]. Other studies that focused on SSRIs "fluoxetine and paroxetine", demonstrated treated via these drugs will stimulate the oxytocin-releasing response to 5-HT_1A agonists without changing in the basal oxytocin levels[52], these findings suggest that some SSRIs' properties may be return to their effects on oxytocin system, and that the chronic intake of oxytocin may be similar to that of SSRIs in anxiety, depressive and satiety paradigm[53-55].

The present results provide the first evidence that oxytocin and serotonin are positively related at peripheral levels, in general, and special correlation was noted at obese human. The obtained outcome results enrich the scientific knowledge with new information about the relationship between the levels of these hormones satisfactory condition have not been touched upon this filed and detail previously. In addition to that, these findings give the several activities regulated by both oxytocin and serotonin levels which may be provide the hypothetical benefits, such new perspectives and insights into psychiatric disorders, social relationship disturbances, and satiety and weight regulation disorders, as well as novel treatment strategies overcoming and/or integrating SSRIs' treatment.

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