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Original Article

# The correlation between plasma levels of oxytocin and betatrophin in non-diabetic and diabetic metabolic syndrome patients: A cross sectional study from Jordan

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ABSTRACT

*Background:* Oxytocin (OXT) is a neurohypophyseal hormone that has been recently shown to possess a number of beneficial effects in diabetes and obesity. Betatrophin is a protein expressed in fat and liver that regulates lipid metabolism and promotes pancreatic β-cell proliferation. It is not investigated yet whether OXT and betatrophin levels correlate in metabolic syndrome (MS) or diabetes patients.
*Methods:* The aim was to assess correlations between plasma betatrophin and OXT levels in MS-diabetic or prediabetic (N = 89) as compared to MS-non-diabetic (N = 69) patients. Competitive binding ELISA was used to evaluate betatrophin and OXT plasma concentrations. Correlations of the above biomarkers and patient clinical characteristics were also detected.
*Results:* As compared to the control MS participants (0.32 ± 0.25 ng/mL); betatrophin plasma levels were increased ($P < 0.001$) in the MS-pre/T2DM patients (1.23 ± 0.68 ng/mL). On the contrary, OXT concentrations were decreased ($P < 0.001$) in the MS-pre/T2DM patients (1222.46 ± 514.55 pg/mL) as compared to the MS control subjects (2323.42 ± 848.68 pg/mL). OXT concentration correlated negatively ($r = -0.492$, $P < 0.001$), while HbA1c and FPG correlated positively with betatrophin plasma levels ($P < 0.001$), but were inversely correlated with OXT levels ($P < 0.001$) in the total sample.
*Conclusion:* Betatrophin levels are increased, while OXT levels are decreased in MS-pre/T2DM. We found an inverse correlation between the levels of the two biomarkers in addition to correlation between their levels and the degree of glycemic control.


## 1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin action, defective insulin secretion or both [1]. Prediabetes is a high-risk condition for diabetes defined by glycemic variables that are higher than normal, but lower than diabetes thresholds [2]. Prediabetes includes impaired fasting glucose (IFG) (FPG levels 100–125 mg/dL [5.6–6.9 mmol/L]), impaired glucose impared glucose tolerance (IGT) (2 h OGTT values of 140–199 mg/dl [7.8–11.0 mmol/l], or glycated hemoglobin (A1c) of 5.7%–6.4%, each of which places individuals at high risk of developing diabetes and its complications.

In recent years, T2DM has been a significant global health issue, which imposes a great burden both on individuals and on health care systems [3].

Metabolic Syndrome (MS) and DM are associated with significant morbidity and mortality, in particular with an excess of cardiovascular deaths [4].

According to the American Diabetes Association (ADA) [5] and the European Association for the Study of Diabetes [6,7], insulin resistance (IR) and MS disorders are strongly associated with many of contributing factors which can be summarized as abdomen white adipose tissue (WAT) accumulation, waist circumference>35 in. (85 cm) in women and >40 in. (100 cm) in men, blood pressure (BP) > 130/85, lipid profile disturbances triglycerides (TG) >150 mg/dL, high density lipoprotein (HDL-C) < 40 mg/dL in men or <50 mg/dL in women and blood glucose levels of >100 mg/dL.

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**Table 1**
Demographic characteristics of study participants.

| Parameter | Total number of subjects[a] N = 158 | MS-Control group N = 69 | MS- pre/T2DM group N = 89 | $P^*$ |
|---|---|---|---|---|
| Age in years (mean ± SD) | 51.16 ± 10.87 | 50.13 ± 10.09 | 52.39 ± 11.07 | 0.198 |
| Range (years) | (20–75) | (24–68) | (24–75) | |
| Gender, N (%)[a] | | | | |
| Male | 53 (33.80%) | 24 (33.30%) | 29 (34.1%) | 0.918 |
| Female | 105(66.20%) | 49 (66.70%) | 56 (65.90%) | |
| BMI (mean ± SD) (Kg/m$^2$) | 33.28 ± 5.24 | 32.71 ± 5.23 | 33.68 ± 5.22 | 0.267 |
| BMI category, N (%)[a] | | | | |
| Normal weight | 4 (2.70) | 3 (4.5) | 1 (1.20) | 0.418 |
| Overweight | 27 (18.10) | 11 (16.40) | 16 (19.50) | |
| Obese | 105 (70.50) | 49 (73.10) | 56 (68.30) | |
| Morbidly obese | 13 (8.70) | 4 (6.00) | 9 (11.00) | |

[a] Percent within total.
[*] *P*-value by independent-sample *t*-test for age, BMI, and gender. BMI: body mass index.

Oxytocin (OXT) is a neurohypophysial hormone representing a nine-amino acid (a.a.) neuropeptide produced by paravetricular and supraoptic hypothalamic OXT neurons. OXT is a hormone with systemic action to mediate reproductive activities including laboring and lactation [8,9], it is secreted in response to different stress stimuli [10,11] and is considered to have effects in the central nervous system (CNS), including social attachment, maternal nurturing as well [12–14]. But the interesting finding was the metabolic benefit action of reversing obesity and all related glucose and insulin disorders in both rat and mouse models [15,16].

Betatrophin is a newly discovered protein of 198 a.a. expressed in fat and liver that promotes β-cell robust proliferation and improves insulin sensitivity in mice [17–19]. It could have a clinical impact on T2DM without the need for pancreatic transplantation and its accompanying immunosuppressive therapy [20,21]. Betatrophin was previously described as angiopoietin-like protein [ANGPTL]-8, TD26, re-feeding-induced fat and liver protein RIFL or lipasin [22]. Its levels are reduced by fasting and are elevated upon insulin resistance and during pregnancy [23]. Additionally, betatrophin concentrations were increased after re-feeding in healthy and diabetic human plasma samples [24] and in type 1 diabetes [20]. Taken together, the aim of the present study was to evaluate a plausible association between plasma levels of oxytocin and betatrophin in metabolic syndrome-diabetes patients in a cross sectional study from Jordan.

## 2. Experimental

This is a cross sectional study performed in outpatients endocrinology clinics of JUH and National Diabetes Center to find the correlation between the OXT and betatrophin blood levels in two groups of overweight/obese patients with MS. The case group included 89 overweight or obese patients (BMI >25 kg/m$^2$) newly diagnosed with prediabetes [1] or T2DM [1] (Table 1) and who were drug naïve. The control group consisted of 69 overweight or obese individuals (BMI >25 kg/m$^2$) without prediabetes/DM (Fig. 1).

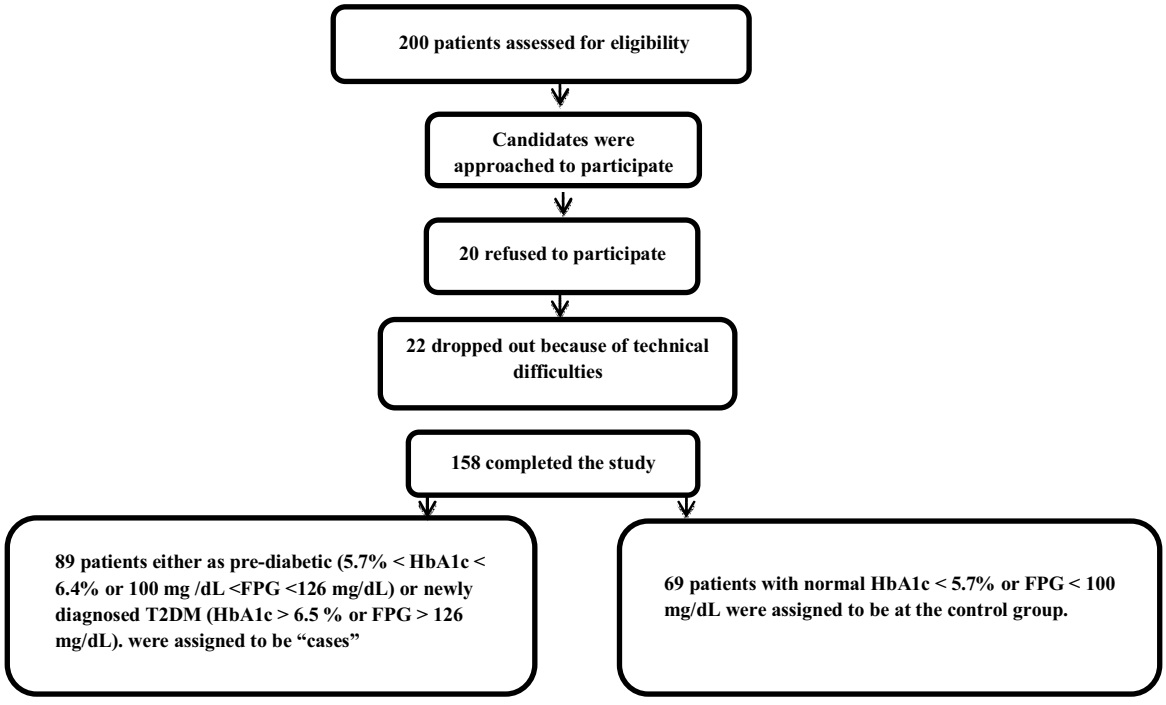


**Fig. 1.** The study flow chart.

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