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# Study of Serum Betatrophin Level as A Novel Endocrinal Regulator Involved in Diabetic Nephropathy Development

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## Abstract

*Background:* Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs. Diabetic Nephropathy (DN) is the leading cause of chronic kidney disease which ultimately progresses to end stage renal disease. Therefore, early diagnostic markers for predicting and monitoring the progression of DN are needed to enable the timely administration of the mostly appropriate protective treatments, we hypothesized that betatrophin may be a novel endocrine regulator involved in DN development.

*Aim of Study:* It was to examine circulating betatrophin level in patients with type 2 diabetes mellitus with or without diabetic nephropathy in comparison with healthy controls.

*Patients and Methods:* The study was carried out on forty patients with type 2 diabetes mellitus. They were recruited from internal Medicine Department of Tanta University Hospital who classified into, 20 type 2 diabetic patients without nephropathy. 20 type 2 diabetic patients with nephropathy. Another twenty apparently healthy subjects were chosen from outpatient clinics of Tanta University Hospital and served as control group. This study was carried out from June 2016 to May 2017. An approval by Ethical Committee of Tanta University Faculty of Medicine was obtained. They were subjected to thorough history taking, clinical examination including anthropometric measurements (sex, age, BMI) and laboratory investigations including glycated Hb, fasting and post prandial blood glucose, liver function tests, UACR, kidney function, lipid profile, serum betatrophin estimation by ELISA.

*Results:* Betatrophin was significantly higher in both $T_2$DM with nephropathy and $T_2$DM as compared to control group and significantly higher in $T_2$DM with nephropathy than $T_2$DM. There was significant positive correlation between betatrophin hormone and $HbA_1c$, BMI, serum total cholesterol, serum triglycerides, LDL and negative correlation with HDL in both $T_2$DM group and $T_2$DM with nephropathy group. There was positive correlation between betatrophin and Albumin/Creatinine Ratio (ACR) in T2DM with nephropathy group.

*Conclusion:* There was no significant correlation between betatrophin and Albumin/Creatinine Ratio (ACR) in $T_2$DM group, while there was positive correlation between betatrophin and ACR in diabetic nephropathy group. Thus, betatrophin may be a novel endocrinal regulator involved in diabetic nephropathy development.

***Key Words:*** *Diabetic Nephropathy – Novel Endocrinal – Serum Betatrophin.*

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## Introduction

**DIABETES** mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Type 2 diabetes mellitus as a metabolic disorder has features such as dyslipidemia, insulin resistance and loss of mass and function of beta cells [1].

Diabetic Nephropathy (DN) is the leading cause of chronic kidney disease which ultimately progresses to end stage renal disease. Therefore, early diagnostic markers for predicting and monitoring the progression of DN are needed to enable the timely administration of the mostly appropriate protective treatments. Furthermore, dysregulated lipid metabolism results in diabetic nephropathy development in patients with type 2 diabetes mellitus [2].

Betatrophin is a newly characterized circulating hormone that is produced in tissues such as adipose tissue and liver and stimulates pancreatic beta-cell proliferation. Moreover, hepatic overexpression of betatrophin leads to increased beta-cell proliferation, islet size, insulin content, and improved glucose homeostasis [3]. It has been implicated in both glucose and lipid metabolism. A number of

studies reported that betatrophin was increased in $T_2DM$ patients, while other studies showed that circulating betatrophin level was reduced in $T_2DM$ patients [4].

*Aim:*

The purpose of the present study is to examine circulating betatrophin level in patients with $T_2DM$ with or without diabetic nephropathy in comparison with healthy controls.

## Subjects and Methods

This study was carried out on 40 patients with type 2 diabetes mellitus (20 $T_2DM$ without nephropathy, 20 $T_2DM$ with nephropathy) and 20 apparently healthy control subjects with age ranged from 20 to 63 years. The patients were selected from those admitted to Internal Medicine Department of Tanta University Hospital. The control subjects were selected from outpatient clinic of Internal Medicine Department.

*Exclusion criteria:* Any evidence of active infection (e.g. fever, or leukocytosis). No known history of other chronic systemic diseases. No long-term medical treatment for other chronic systemic diseases.

Studied groups were subjected to full history taking, clinical examination including anthropometric measurements (sex, age, weight and height for Body Mass Index (BMI) and laboratory investigations including glycated Hb, liver function tests, UACR, kidney function tests, fasting blood glucose, post prandial blood glucose, lipid profile and serum betatrophin estimation by ELISA.

## Results

This study included 60 subjects divided into group I: This group included 20 apparently healthy subjects, group II: Included 20 patients type 2 diabetes mellitus without nephropathy, group III: Included 20 type 2 diabetic patients with nephropathy.

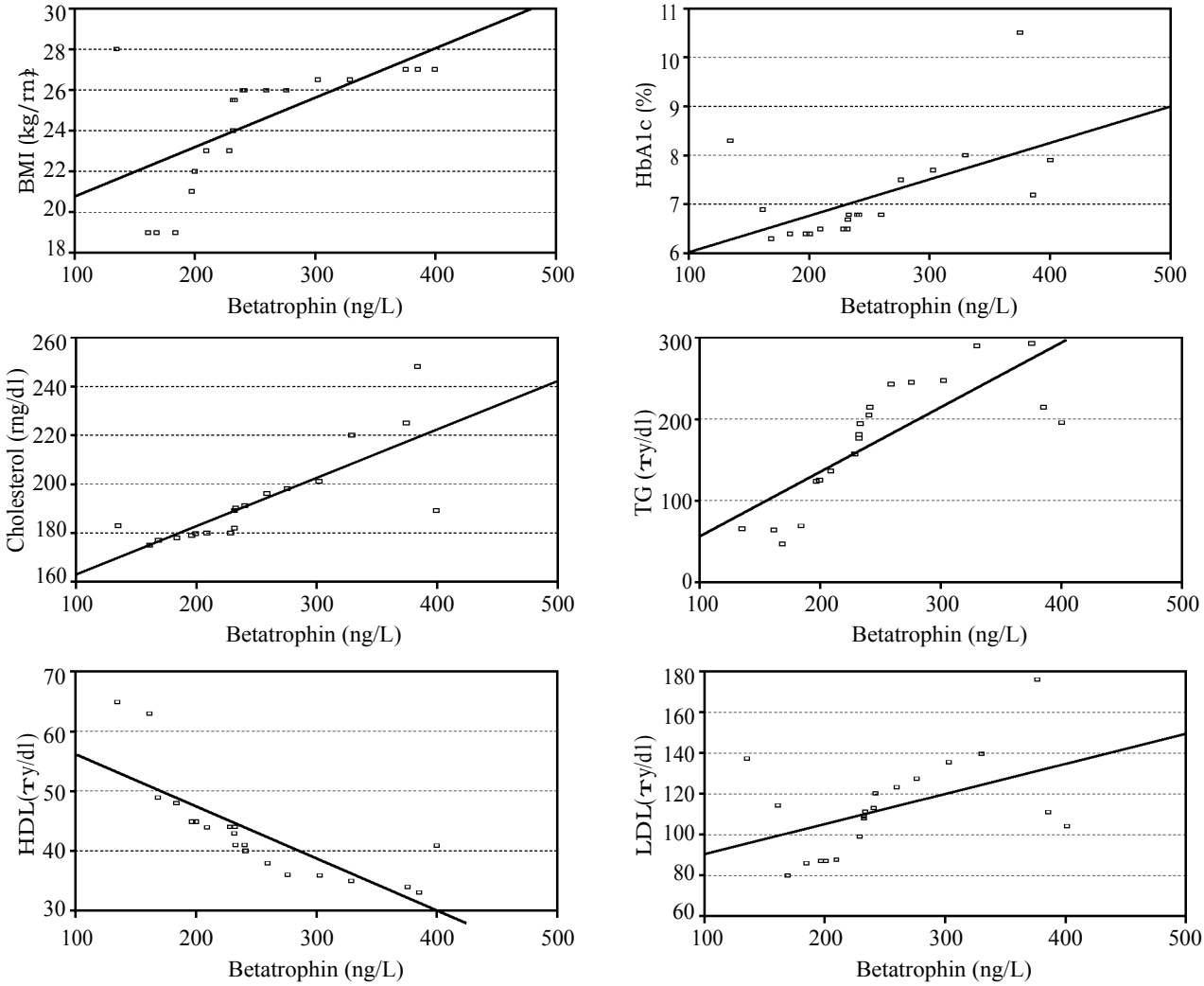


Fig. (1): Correlation between betatrophin and BMI, $HbA_1c$, TG, total cholesterol, HDL, LDL in group II.

Table (1): Age and duration of diabetes mellitus in studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *Age (years):* | | | | | |
| Group I | 23-60 | 47.65±9.58 | 0.776 | 0.465 | $p_1$ 0.940 |
| Group II | 36-60 | 47.45±7.73 | | | $p_2$ 0.303 |
| Group III | 36-63 | 50.40±7.65 | | | $p_3$ 0.270 |
| *Duration of DM (years):* | | | | | |
| Group II | 4-10 | 6.55±1.96 | 10.296 | 0.001* | |
| Group III | 10-25 | 17.95±4.55 | | | |

There was no significant difference between studied groups as regard the age ($p$>0.05), while there was significant difference between group II and group III as regard the duration of diabetes mellitus ($p$<0.05).

Table (2): Gender distribution of studied groups.

| Gender | Group I | Group II | Group III | Total |
|---|---|---|---|---|
| *Male:* | | | | |
| N | 10 | 7 | 8 | 25 |
| % | 50.0% | 35.0% | 40.0% | 41.7% |
| *Female:* | | | | |
| N | 10 | 13 | 12 | 35 |
| % | 50.0% | 65.0% | 60.0% | 58.3% |
| *Total:* | | | | |
| N | 20 | 20 | 20 | 60 |
| % | 100.0% | 100.0% | 100.0% | 100.0% |
| *Chi $_2$ quare:* | | | | |
| $\chi$ | | 0.960 | | |
| *p*-value | | 0.619 | | |

There was no significant difference between studied groups as regard gender ($p$>0.05).

Table (3): BMI distribution of studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *BMI (kg/m$^2$):* | | | | | |
| Group I | 18-25 | 20.50±1.95 | 24.175 | 0.001* | $p_1$ 0.002* |
| Group II | 19-28 | 24.30±3.04 | | | $p_2$ 0.001 * |
| Group III | 21-40 | 28.65±5.31 | | | $p_3$ 0.001* |

There was significant increase of BMI in group III and group II compared to group I and in group III compared to group II ($p$<0.05).
Significance = $p$<0.05.
Non significance = $p$>0.05.

Table (4): Glucose profile of studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *FBS (mg/dl):* | | | | | |
| Group I | 72-96 | 81.60±6.75 | 24.580 | 0.001* | $p_1$ 0.001* |
| Group II | 88-210 | 137.45±35.11 | | | $p_2$ 0.001 * |
| Group III | 74-280 | 164.30±55.38 | | | $p_3$ 0.030* |
| *PPS (mg/dl):* | | | | | |
| Group I | 92-123 | 105.55±8.96 | 21.626 | 0.001* | $p_1$ 0.001* |
| Group II | 100-474 | 207.70±85.30 | | | $p_2$ 0.001 * |
| Group III | 155-520 | 238.60±78.07 | | | $p_3$ 0.150 |
| *HbA1c (%):* | | | | | |
| Group I | 4.8-5.9 | 5.29±0.32 | 71.154 | 0.001* | $p_1$ 0.001* |
| Group II | 6.3-10.5 | 7.15±0.99 | | | $p_2$ 0.001 * |
| Group III | 7.2-12.8 | 9.75±1.77 | | | $p_3$ 0.001* |

As regard fasting blood glucose, HbA1 c there was significant increase in group III and group II compared to group I and in group III compared to group II ($p$<0.05).

As regard post prandial blood glucose there was significant increase in group III and group II compared to group I ($p$<0.05), while there was no significant difference between group III compared to group II ($p$>0.05).

Table (5): Kidney functions of studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *Urea (mg/dl):* | | | | | |
| Group I | 15-26 | 18.55±3.72 | 66.386 | 0.001 * | $p_1$ 0.166 |
| Group II | 18-40 | 30.15±7.73 | | | $p_2$ 0.001* |
| Group III | 30-210 | 106.30±44.50 | | | $p_3$ 0.030* |
| *Creatinine (mg/dl):* | | | | | |
| Group I | 0.6-1.1 | 0.80±0.15 | 36.386 | 0.001 * | $p_1$ 0.461 |
| Group II | 0.7-1.4 | 1.15±0.20 | | | $p_2$ 0.001* |
| Group III | 1.8-8.6 | 4.43±2.56 | | | $p_3$ 0.001* |
| *Urine albumin /creatinine ratio (ACR) (mg alb./ g.creat.):* | | | | | |
| Group I | 15-22 | 19.25±2.05 | 16.945 | 0.00 1* | $p_1$ 0.933 |
| Group II | 17-29 | 23.37±3.60 | | | $p_2$ 0.001* |
| Group III | 38-722 | 269±268.8 | | | $p_3$ 0.001* |

As regard blood urea,serum creatinine, ACR there was significant increase in group III compared to group I and group II ($p$<0.05), while there was no significant difference between group I and group II ($p$>0.05).
Significance = $p$<0.05.
Non significance = $p$>0.05.

Table (6): Lipid profile of studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *Cholesterol (mg/dl):* | | | | | |
| Group I | 120-180 | 135.45±17.94 | 40.582 | 0.001 * | $p_1$ 0.001* |
| Group II | 157-248 | 192.6±18.71 | | | $p_2$ 0.001* |
| Group III | 169-372 | 240.7±58.69 | | | $p_3$ 0.001* |
| *TG (mg/dl):* | | | | | |
| Group I | 41-95 | 65.45±16.44 | 28.511 | 0.001 * | $p_1$ 0.001* |
| Group II | 47-293 | 174.45±74.59 | | | $p_2$ 0.001* |
| Group III | 67-350 | 236.48±99.71 | | | $p_3$ 0.009* |
| *HDL (mg/dl):* | | | | | |
| Group I | 36-64 | 48.10±9.85 | 10.892 | 0.001 * | $p_1$ 0.089 |
| Group II | 33-65 | 43.25±8.41 | | | $p_2$ 0.001* |
| Group III | 23-52 | 35.15±8.25 | | | $p_3$ 0.005* |
| *LDL (mg/dl):* | | | | | |
| Group I | 47-89 | 61.55±10.99 | 46.392 | 0.001 * | $p_1$ 0.001* |
| Group II | 80-176 | 112.73±23.17 | | | $p_2$ 0.001* |
| Group III | 110-241 | 175.98±49.34 | | | $p_3$ 0.001 |

As regard total cholesterol, serum triglycerides and LDL there was significant increase in group III and group II compared to group I and in group III compared to group II ($p$<0.05).

As regard HDL there was significant decrease in group III compared to group I and group II ($p$<0.05), while there was no significance difference between group I and group II ($p$>0.05).
Significance = $p$<0.05.
Non significance = $p$>0.05.

Table (7): Betatrophin concentration of studied groups.

| | Range | Mean ± SD | F.test | *p*-value | |
|---|---|---|---|---|---|
| *Betatrophin (ng/L):* | | | | | |
| Group I | 20-290 | 182.33±74.21 | 57.571 | 0.001* | $p_1$ 0.024* |
| Group II | 135-400 | 249.50±74.95 | | | $p_2$ 0.001* |
| Group III | 512-93 8.4 | 659.01±119.27 | | | $p_3$ 0.001* |

Significance = $p$<0.05. Non significance = $p$>0.05.

There was significant increase in group II and group III compared to group I and in group III compared to group II ($p$<0.05).

Table (8): Correlation between betatrophin and different parameters in group II.

| | Betatrophin (ng/L) | |
|---|---|---|
| | *r.* | *p* |
| BMI (kg/m$^2$) | 0.479 | 0.035* |
| HbA1c (%) | 0.460 | 0.041* |
| Albumin/creatinine ratio (ACR) (mg. alb/g.creat) | 0.251 | 0.243 |
| Cholesterol (mg/dl) | 0.633 | 0.003* |
| TG (mg/dl) | 0.588 | 0.006* |
| HDL (mg/dl) | –0.560 | 0.010* |
| LDL (mg/dl) | 0.476 | 0.03 4* |

There was significant positive correlation between betatrophin hormone and HbA1c, BMI, serum total cholesterol, serum triglycerides and LDL in group II ($p$<0.05), while negative correlation was found between betatrophin and HDL ($p$<0.05). There was no significant correlation between betatrophin and albumin/creatinine ratio (ACR) in group II ($p$>0.05).

Table (9): Correlation between betatrophin and different parameters in group III.

| | Betatrophin (ng/L) | |
|---|---|---|
| | *r.* | *p* |
| BMI (kg/m$^2$) | 0.627 | 0.003* |
| HbA1c (%) | 0.939 | 0.001* |
| Albumin/creatinine ratio (ACR) (mg alb./g creat.) | 0.509 | 0.025* |
| Cholesterol (mg/dl) | 0.636 | 0.003* |
| TG (mg/dl) | 0.475 | 0.034* |
| HDL (mg/dl) | –0.771 | 0.001* |
| LDL (mg/dl) | 0.476 | 0.034* |

There was significant positive correlation between betatrophin hormone and HbA1 c, BMI, serum total cholesterol, serum triglycerides and LDL in group II ($p$<0.05), while negative correlation was found between betatrophin and HDL ($p$<0.05). There was no significant correlation between betatrophin and albumin/creatinine ratio (ACR) in group II ($p$>0.05).

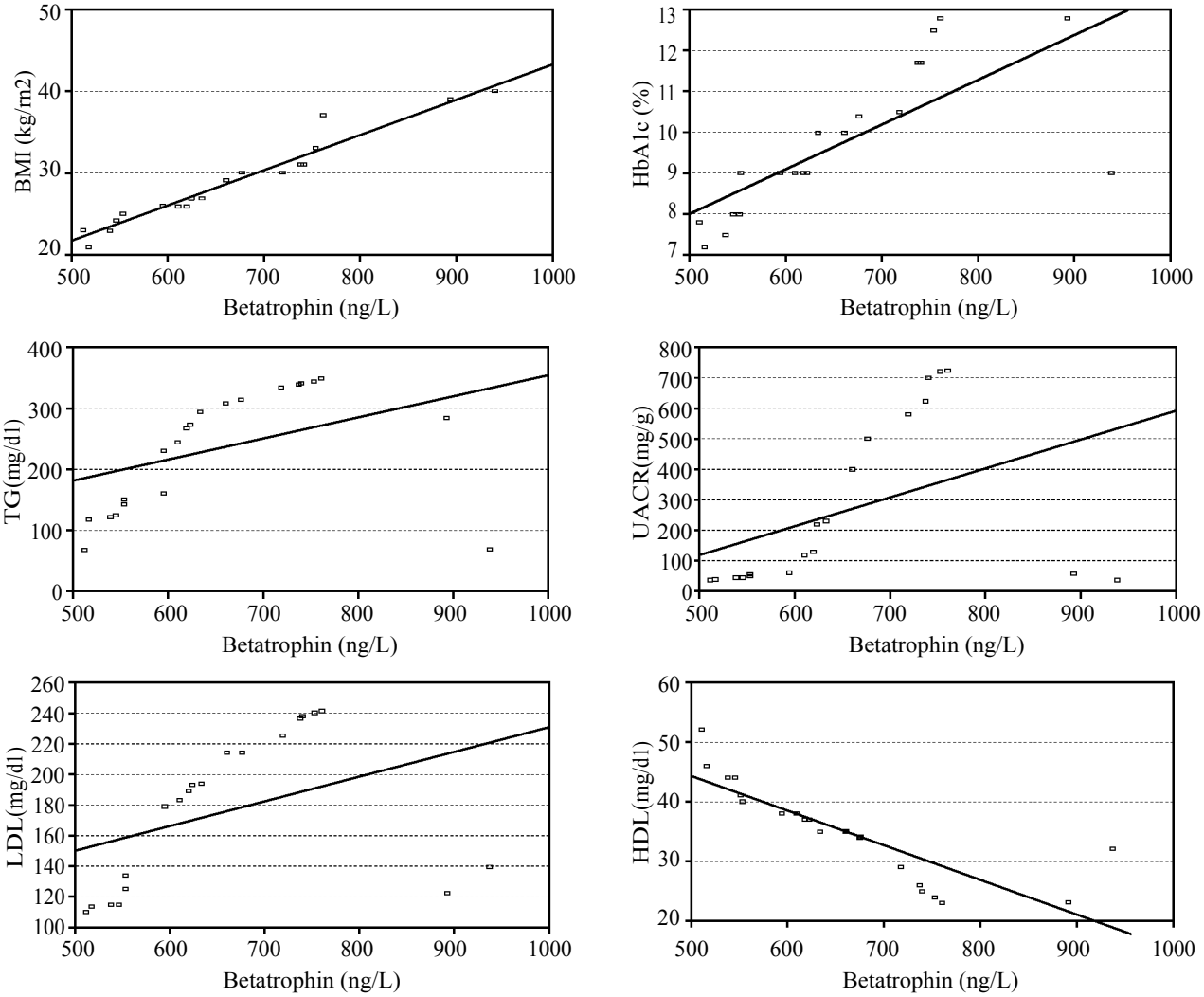


Fig. (2): Correlation between betatrophin and BMI, HbA $_1$c, TG, total cholestrol, LDL, HDL in group III.

## Discussion

The present study showed that there was no significant difference as regard age and sex between the three studied groups. This is in accordance with Hassan Ghasemi et al., [5] who found that there was no significant difference in age and sex between T2DM without nephropathy and control

group. On the other hand Chang-Chiang et al., [6] reported significant increase in age in $T_2DM$ with nephropathy in comparison with control group.

In the present study, there was significant difference between the two groups of diabetic patients as regard disease duration. This is in agreement with Chang-Chiang et al., who found that the mean value of disease duration show significant difference, and explained that the duration of disease represent risk factor for DN development and serum betatrophin level was significantly increased in the type 2 diabetic patients with more than five years duration of DM.

The results of the present study revealed that there was significant difference between the studied groups as regard BMI. This is in agreement with Chang Chiang et al., and this in disagreement with Hassan Ghasemi et al., who found that there was no significant difference in BMI between $T_2DM$ without nephropathy and control group.

Moreover, results of this work showed that there was significant difference in fasting blood glucose, post prandial blood glucose and HbA1c levels between the studied groups. This is in accordance with Chang-Chiang et al., Hassan Ghasemi et al., and Zhang and Abou-Samra [7].

Hassan Ghasemi et al., explained the high levels of $HbA_1c$ in $T_2DM$ with nephropathy group by the lack of glycemic control and the high $HbA_1c$ would lead to more renal damage and development of DN.

As regard serum creatinine and blood urea there was significant increase in diabetic nephropathy patients as compared with control subjects and $T_2DM$ patients without nephropathy, while there was no significance difference between healthy subjects and $T_2DM$ patients without nephropathy. This is in disagreement with Bamanikar et al., [8] who reported statistically significant increase in creatinine level in $T_2DM$ without nephropathy group compared to control group.

As regard the Albumin Creatinine Ratio (ACR), there was statistically significant increase in patients with diabetic nephropathy compared to $T_2DM$ without nephropathy and control group. This is in agreement with Chang-Chiang et al., who reported significance increase in ACR between $T_2DM$ with nephropathy compared to control group.

Satchell and Tooke [9] explained mechanism of progression of albuminuria in diabetic nephropathy by the following pathological changes: Parallel changes occur in the glomerular filtration barrier with glomerular endothelial cell injury, with loss of glycocalyx and cell apoptosis. The glycocalyx is an aqueous extracellular layer that covers the glomerular capillary lumen side, and plays an important role in glomerular vascular function and permeability. Further thickening of the glomerular basement membrane and podocyte foot process effacement and loss of podocytes in the urine are other mechanisms that characterize the alteration of the permeability properties of the glomerular filtration barrier and disease progression. Podocyte detachment has been positively correlated with urinary albumin excretion and increasing podocyte detachment is associated with decreased permselectivity of the glomerulus and progressive albuminuria.

The results of the present study revealed that there was significant difference between the diseased groups and control group as regard serum total cholesterol. This is in agreement with Hassan Ghasemi et al., who suggested that, these results were based on the association of $T_2DM$ with an atherogenic lipid profile and the risk of cardiovascular disorders.

Opposite to this work, Chang-Chiang et al., reported that there was no statistically significant difference in serum total cholesterol between $T_2DM$ with nephropathy group and control group. They suggested that, this result may be related to duration of type 2 diabetes mellitus and medications received by diabetic patients.

As regard serum triglycerides, there was significant difference between the diseased groups and healthy group. This is in agreement with Chang-Chiang et al., who explained the increase in serum triglycerides in diabetic nephropathy group by dysregulated lipid metabolism results in diabetic nephropathy development in patients with type 2 diabetes mellitus. This may be due to accumulation of lipids in kidney which causes increased advanced glycation end-products, inflammatory cytokines, and reactive oxygen species resulted in endothelial dysfunction, glomerulosclerosis and tubulointerstitial injury in $T_2DM$.

Additionally, in accordance with our results Agnieszka et al., [10] and Zhang et al., reported that serum triglycerides were also significantly higher in patients with $T_2DM$ without nephropathy than in the control group and they explained that high level of betatrophin in diabetic patients suppressed adipose triglyceride lipase activity and

increased triglycerides accumulation in hepatocytes, adipocytes, and beta cells [10].

In the present study there was significant decrease in HDL in diabetic nephropathy patients as compared with control group and $T_2$DM without nephropathy group, while there was no significance difference between healthy subjects and $T_2$DM patients without nephropathy. As regard low density lipid there was significant increase in its level in the diseased groups as compared to healthy group.

This is in agreement with studies of Chang-Chiang et al., and Hassan Ghasemi et al., who found that HDL was lower in the group with nephropathy than in healthy group. On contrary to these findings Quagliarini et al., [11] suggested decreased both HDL and LDL levels in $T_2$DM.

As regard betatrophin hormone, there was statistically high significant difference in its levels between $T_2$DM patients without nephropathy and $T_2$DM with nephropathy patients. Also, there was statistically highly significant difference between the two patient groups and the healthy control group as regard betatrophin. This is in agreement with Chang-Chiang et al., who reported that circulating betatrophin was significantly high in $T_2$DM with nephropathy patients in comparison with healthy control group, also Hassan Ghasemi et al., Yi et al., and Fu et al., [12] reported that circulating betatrophin levels were significantly higher in patients with $T_2$DM without nephropathy than in the normal subjects [12].

Yi et al., concluded that, betatrophin induce pancreatic beta cell proliferation, so over expression of betatrophin play role in improving glucose tolerance and being anticipated as a therapeutic strategy as a glucose lowering drug in DM [15].

Amnah et al., [13] reported that pancreatic beta cell repopulation was one of the anticipated treatments for both diabetes type 1 and type 2 patients. Also, they reported that injecting the human betatrophin directly into the islets of mice increased replication of pancreatic beta cells. In this regard, they suggested that betatrophin emerged as one of the possible drug targets due to its high pancreatic beta cell proliferative specificity and significant magnitude of proliferation.

Fenzl et al., [14] reported no changes in betatrophin level related to $T_2$DM, while Gomez-Ambrosi et al., studies showed that circulating betatrophin level was reduced in $T_2$DM patients. These different results may be attributed to methodological differences between the immunoassays or to dissimilarities between the subjects' characteristics.

Daniel et al., [15] reported that serum betatrophin concentration was increased in type 1 diabetes. They reported that there was already a potential stimulus for beta cell proliferation present in type 1 diabetes, but they suggested that, this was not sufficient to counteract the decline in C peptide levels in the long run.

Amnah et al., reported that increased serum betatrophin has been observed in several diseases including diabetes mellitus, metabolic syndrome and non-alcoholic fatty liver disease. In this regard, they suggested that inhibition of betatrophin for reducing the serum triglyceride levels and its over expression for improving glucose tolerance was being anticipated as a therapeutic strategy to lower the triglycerides levels in dyslipidemia and as a glucose lowering drug in DM.

Agnieszka et al., reported increased levels of serum betatrophin in $T_2$DM, type 1 diabetes mellitus and gestational diabetes, whereas other data reported decreased serum betatrophin concentrations in obese individuals.

In the present study, there was significant positive correlation between betatrophin hormone and $HbA_1c$, BMI, serum total cholesterol, serum triglycerides, LDL and negative correlation with HDL in both diabetic groups. These results are in accordance with study of Chang-Chiang et al., as regard positive and negative correlation except that they reported negative correlation between betatrophin hormone and serum total cholesterol in diabetic nephropathy patients.

In parallel with this study Hassan Ghasemi et al., Agnieszka et al., Amnah et al., and Lukas et al., [16] concluded that, there was positive correlation between serum betatrophin and multiple parameters including serum triglycerides, serum total cholesterol and $HbA_1c$ in diabetic patients with and without nephropathy [16].

Agnieszka et al., suggested that betatrophin has an impact on lipid metabolism. In experimental data, betatrophin suppressed adipose triglyceride lipase activity and increased TG accumulation in hepatocytes and beta cells.

Javier et al., [17] reported that betatrophin operated as a blood lipid regulator by modulating serum triglyceride levels and that its hepatic expression was reduced by fasting and restored by refeeding. They suggested that betatrophin induced

triglyceride elevation through reduced triglyceride clearance by lipoprotein lipase inhibition. Moreover, betatrophin overexpression increased triglyceride levels, whereas betatrophin deficiency reduced triglyceride concentrations associated with both a reduction in very low-density lipoprotein secretion and an increase in lipoprotein lipase activity.

Quagliarini et al., reported that betatrophin concentrations in obese humans were greatly reduced and negatively correlated with triglyceride levels and positively correlated with HDL-cholesterol. Their explanation depended on, betatrophin levels may be decreased in response to the increased lipidemia as a compensatory mechanism aimed at reducing lipoprotein levels, while Guo et al., **[18]** reported that serum betatrophin levels did not differ between lean and obese or between Normal Glucose Tolerance (NGT) and $T_2$DM participants.

In addition, there was no significant correlation between betatrophin and Albumin/Creatinine Ratio (ACR) in $T_2$DM without nephropathy, while there was significant positive correlation between betatrophin hormone and Albumin/Creatinine Ratio (ACR) in $T_2$DM with nephropathy. These results are in consistent with Chang-Chiang et al., who concluded that; betatrophin may serve as predictor of diabetic nephropathy.

Mohammed and Khazaal., **[19]** suggested that betatrophin level had no statistically significant differences between non-diabetics and diabetics and serum betatrophin levels had no statistically significant positive or negative correlations with age, anthropometric, lipid profile,diabetic parameters. They explained the discrepancy between results depend on the following observations; first, duration of $T_2$DM where investigators reported that people with longer duration of diabetes had greater betatrophin levels. Second, half subjects with $T_2$DM receiving medication. Moreover, medications such as metformin could possibly modify the degree of insulin resistance and then affect the relation between betatrophin and insulin resistance. Third, differences in sample size, ethnic groups and sampling. Fourth, a potential diverse grade of inflammation may also exert a discrepancy impact because it impinges on both glucose and lipid metabolism.

*Conclusion:*

The current study showed statistically significant increased circulating betatrophin concentrations in type 2 diabetic patients, in particular type 2 diabetic patients with nephropathy. There was positive correlation between betatrophin and $HbA_1c$, BMI, serum total cholesterol, serum triglycerides, LDL and negative correlation with HDL in both diabetic groups. There was no significant correlation between betatrophin and Albumin/ Creatinine Ratio (ACR) in $T_2$DM group, while there was positive correlation between betatrophin and ACR in diabetic nephropathy group.

Thus, betatrophin may be a novel endocrinal regulator involved in diabetic nephropathy development.

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*Conflicts of interest:*

No conflicts of interest declared.

*Authors' contributions:*

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

## References

1- TUOMI T., SANTORO N., CAPRIO S., et al.: The many faces of diabetes a disease with increasing heterogeneity. Lancet, 383: 1084-94, 2014.

2- ATSUKO K., TAKESHI S. and DAISUKE I.: Urinary liver type fatty acid binding protein in diabetic nephropathy. Clinica Chimica Acta, 424: 104-8, 2013.

3- YI P., PARK J.S. and MELTON D.A.: Betatrophin: A hormone that controls pancreatic beta cell proliferation. Cell, 153: 747-58, 2013.

4- GOMEZ-AMBROSI J., PASCUAL E., CATALAN V., et al.: Circulating betatrophin concentrations are decreased in human obesity and type 2 diabetes. J. Clin. Endocrinol. Metab., 99: E2004-9, 2014.

5- HASSAN GHASEMI, HEIDAR TAVILANI, IRAJ KHODADADI, et al.: Circulating Betatrophin Levels Are Associated with the Lipid Profile in Type 2 Diabetes Chonnam. Med. J., 51: 115-9, 2015.

6- CHANG-CHIANG C., HENDRA S., WEN-HAN C., et al.: Higher serum betatrophin level in type2 diabetes subjects is associated with urinary albumin excretion and renal function: Cardiovasc. Diabetol., 15: 3, 2016.

7- ZHANG R. and ABOU-SAMRA A.B.: Emerging roles of Lipasin as a critical lipid regulator. Biochem. Biophys. Res. Commun., 432: 401-5, 2013.

8- BAMANIKAR S., BAMANIKAR A. and ARORA A.: Study of Serum urea and Creatinine in Diabetic and non-diabetic patients in in a tertiary teaching hospital The Journal of Medical Research, 2 (1): 12-5, 2016.

9- SATCHELL S. and TOOKE J.: What is the mechanism of microalbuminuria in diabetes: A role for the glomerular endothelium? Diabetologia, 51: 714-25, 2008.

10- AGNIESZKA A., AGNIESZKA L., MALGORZATA J., et al.: Serum Concentrations of Betatrophin and Its Association with Indirect Indices of Insulin Resistance and Beta Cell Function in Women with Polycystic Ovary Syndrome. Hindawi International Journal of Endocrinology, Article ID 2316986, 6 pages, 2017.

11- QUAGLIARINI F., WANG Y., KOZLITINA J., et al.: Atypical angiopoietin-like protein that regulates ANGPTL3. Proc. Natl. Acad. Sci. USA, 109: 19751-6, 2012.

12- FU Z., BERHANE F., FITE A., et al.: Elevated circulating lipasin/betatrophin in human type 2diabetes and obesity. Sci. Rep., 4: 5013, 2014.

13- AMNAH S., ELISA C., SAMAR H., et al.: Visualizing the regulatory role of Angiopoietin-like protein 8 (ANGPTL8) in glucose and lipid metabolic pathways. Genomic, YGENO-08894; No. of Pages: 11; 4C, 2017.

14- FENZL A., ITARIU B.K., KOSI L., et al.: Circulating betatrophin correlates with atherogenic lipid profiles but not with glucose and insulin levels in insulin-resistant individuals. Diabetologia, 57: 1204-8, 2014.

15- DANIEL E., JOEY L. and CARLSSON.: PO Increased circulating levels of betatrophin in individuals with long-standing type 1 diabetes Diabetologia, 57: 50-3, 2014.

16- LUKAS M., FRANZISKA S., ANTJE F.R., et al.: Renal function is independently associated with circulating betatrophin. PLOS ONE, Journal.pone.0173197 1:10, 2017.

17- JAVIER G.A., EIDER P., VICTORIA C., et al.: Circulating Betatrophin Concentrations Are Decreased in Human Obesity and Type 2 Diabetes Clin. Endocrinal. Metab., 99 (10): E2004-E2009, 2014.

18- GUO K., LU J., YU H., et al.: Serum betatrophin concentrations are significantly increased in overweight but not in obese or type diabetic individuals. Obesity, 23 (4): 793-7, 2015.

19- MOHAMMED A.K. and KHAZAAL F.A.K.: Betatrophin is correlated with glucagon and insulin release rather thaninsulin resistance marker in type 2 diabetes mellitus Iraqi women. International Journal of Research in Medical Sciences, 4 (10): 4264-71, 2016.

# دراسة مستوى البيتاتروفين كمنظم غددى جديد فى حالات تطور إعتلال الكلى السكرى

يمثل داء السكرى مجموعة من الأمراض الآيضية ويتميز بإرتفاع نسبة السكر فى الدم وهو ناتج عن نقص فى إفراز الآنسولين آو عمل الآنسولين آو كليهما. يؤدى إرتفاع نسبة السكر على المدى البعيد إلى الإضرار بالعديد من الآعضاء. إعتلال الكلية السكرى السبب الرئيسى لآمراض الكلى المزمنة التى تتقدم فى نهاية المطاف إلى المرحلة النهائية فى الفشل الكلوى لذلك، هناك حاجة إلى علامات التشخيص المبكر للتنبؤ ورصد إعتلال الكلى السكرى لتمكين تطبيق آنسب العلاجات الوقائية فى الوقت المناسب.

\الهدف: تحديد مستوى بيتاتروفين فى السيرم عند المرضى الذين يعانون من داء السكرى من النوع الثانى والمصاحب بوجود آو عدم إعتلال الكلى السكرى مقارنة بمجموعة من الآصحاء غير المصابين كمجموعة ضابطة.

\المرضى وطرق البحث: آجريت هذه الدراسة على آربعين مريضا مصابين بداء السكرى من النوع ٢، وتم حجزهم بقسم الباطنة بمستشفى جامعة طنطا الذين صنفوا إلى مجموعتين: الآولى ٢٠ مريضا مرضى السكرى من النوع ٢ دون إعتلال الكلية، الثانية ٢٠ مريضا من النوع ٢ يعانون من إعتلال الكلية السكرى، ٢٠ شخصا من الآصحاء كمجموعة ضابطة. وقد خضعت المجموعات للآتى: القياسات الإنسانية (الجنس والعمر ومؤشر كتلة الجسم) والفحوص المختبرية بما فى ذلك الجلوكوز السكرى وإختبارات وظائف الكبد ونسبة الآنسولين للكرياتينين فى البول وإختبارات وظائف الكلى وسكر صايم وساعتين بعد الآكل والدهون. قياس نسبة السيرم بيتاتروفين بإستخدام تقنية الإليزا.

\النتائج: كشفت هذه الدراسة عن: إرتفاع مستوى البيتاتروفين فى المرضى الذين يعانون من مرض السكرى من النوع الثانى مقارنة بالآصحاء، آيضا كان المستوى عاليا فى مرضى إعتلال الكلى السكرى مقارنة بمرضى السكرى من النوع الثانى الغير مصاحب بإعتلال الكلى السكرى . كما وجد آن مستوى البيتاتروفين فى الدم يتناسب طرديا مع الجلوكوز السكرى ومؤشر كتلة الجسم ومستوى الكوليسترول والدهون الثلاثية والبروتينات منخفضة الكثافة ويتناسب عكسيا مع البروتينات عالية الكثافة وذلك فى كلا من مرضى السكرى من النوع الثانى، مرضى إعتلال الكلى السكرى. كما آن مستوى البيتاتروفين يتناسب طرديا مع نسبة الآلبيومين للكرياتينين وذلك فى مرضى إعتلال الكلى السكرى فقط.

\الإستنتاج: مستوى البيتاتروفين يتناسب طرديا مع نسبة الآلبيومين للكرياتينين وذلك فى مرضى إعتلال الكلى السكرى فقط لذلك يمكن إعتبار البيتاتروفين هرمون غددى جديد يساعد فى تشخيص إعتلال الكلى السكرى.

\التوصيات: ونحن نوصى بالمزيد من الدراسات على مدى آوسع من المرضى بآعمار مختلفة لتحديد وإيضاح دور البيتاتروفين فى مرضى إعتلال الكلى السكرى.