SERUM VISFATIN RELATIONSHIP WITH GLYCEMIC CONTROL AND ADIPOSY Indices IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

OBJECTIVE: To assess and compare serum visfatin levels with body composition adiposity indices and glycemic control in patients with Type 2 Diabetes Mellitus (T2DM).

METHODS: This observational case-control study was conducted at the Department of Physiology, College of Medicine and King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia from April 2018 to March 2019. We studied sixty three individuals (33 T2DM and 30 controls) who were recruited from diabetes care clinics. Anthropometric, demographic and clinical characteristics were recorded from all participants and they were matched for age and gender. Venous blood samples were collected to measure visfatin and glycosylated hemoglobin (HbA1c). Adiposity indices were analyzed by Bio Impedance Analyzer (BIA).

RESULTS: Serum visfatin levels were 7.01±3.79 ng/ml in subjects with T2DM and 4.02±2.74 ng/ml in healthy subjects (p=0.046). Body composition indices including BMI, BMR, body fat percentage [BF%], body fat mass [BFM], truncal fat [TF], truncal fat mass [TFM] and visceral fat [VF] differences were not statistically significant between two groups. Serum visfatin levels were 9.29±3.44 ng/ml in T2DM with poor glycemic control (HbA1c >7.5%) as compared to 4.24±1.87 ng/ml in diabetic patients with good glycemic control (HbA1c <7.5%) (p=0.001). Visfatin positively correlated with BMI (r=0.284, p<0.05), BF% (r=0.302, p<0.05), BFM (r=0.280, p<0.05), VF (r=0.263, p<0.05) and HbA1c (r=0.394, p<0.01).

CONCLUSION: The results of this study show that T2DM patients have high serum visfatin levels. Moreover, higher levels of visfatin are observed with poor glycemic control and increasing body adiposity indices.

KEY WORDS: Diabetes Mellitus, Type 2 (MeSH); Visfatin (Non-MeSH); Nicotinamide Phosphoribosyltransferase (MeSH); Glycemic control (MeSH); Body fat percentage (Non-MeSH); Intra-Abdominal Fat (MeSH); Visceral fat (Non-MeSH).

THIS ARTICLE MAY BE CITED AS: Habib SS, Bashir S, Habib SH. Serum visfatin relationship with glycemic control and adiposity indices in patients with type 2 diabetes mellitus. Khyber Med Univ J 2020;12(4): 263-7. DOI: 10.35845/kmuj.2020.20254.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is an illness with multiple ramifications. Recent studies discovered a novel adipokine; visfatin [Nicotinamide Phosphoribosyltransferase (NAMPT) or pre-B-cell colony-enhancing factor 1 (PBEF)] that are linked to T2DM which binds to insulin receptors inducing glucose utilization. It is mostly found in visceral adipocytes which explains its up-regulation in obesity. Visfatin has been reported to be high in T2DM and plays an important role in the body’s immune responses, metabolism and inflammation. Tumor Necrosis Factor-Alpha (TNF-α) released from glial cells is triggered by visfatin, which causes neuroinflammation. Animal studies suggest that intracerebroventricular injection of visfatin leads to an illness responses, fever, reduced motor activity, melanocortin and also effects feeding behaviour. It is reported that there is imbalance between the protective and pro-inflammatory adipokines in T2DM, regarded as dysfunction of adipose tissues. This may be partly responsible for promoting diabetes complications. The role of favorable adipokines such as adiponectin, tumor necrosis factor-related proteins, omentin and unfavorable ones like visfatin and resistin, for diagnosis and prognosis of development of cardiovascular diseases in T2DM patients are reviewed in detail. A strong positive correlation has been reported between visfatin level and the inflammatory markers IL-6, TNF- and CRP in T2DM. There is also a positive correlation with insulin resistance and BMI which indicates association of visfatin with obesity and T2DM. High serum leptin, resistin and visfatin in the first trimester of pregnancy are significantly altered leading to the development of gestational diabetes mellitus (GDM). Therefore, these serum markers may serve as significant predictive indices in GDM. Although the relationship of visfatin with obesity has been studied, the relationship of body adiposity indices and relation with the glycemic
control has not been studied in detail. Therefore, in this study we aimed to study and compare serum visfatin levels with body adiposity and glycemic control in patients with T2DM.

**METHODS**

This observational case control study was conducted at Department of Physiology, College of Medicine and King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia from April 2018 to March 2019. The ethical approval was obtained from the Institutional Review Board, College of Medicine and KKUH. A total of 75 subjects, were recruited by convenience sampling from the outpatient clinics of KKUH, out of which 63 were finally selected as per our inclusion criteria (33 T2DM and 30 controls). The groups were matched for age and gender (male 39 and Females 24) Subjects included had age range between 30 to 65 years and were diagnosed cases of T2DM per recent American Diabetes Association (ADA) criteria (American Diabetes Association, 2010) for at least one-year duration. All patients at the time of recruitment were in a stable metabolic state. Any patient with history of cognitive impairment or psychiatric disease (anxiety and depression), liver or renal dysfunction, acute diabetic state (diabetic ketoacidosis and hyperosmolar hyperglycemic state) and pregnancy was excluded from the study. Control group included healthy subjects from hospital staff and patients companions without any history of any ongoing acute or chronic illness. They were matched for gender, age, BMI and social status. All were having normal glucose and glycosylated hemoglobin (HbA1c) levels. The T2DM patients were divided into good and poor glycemic control group based on a cut-off HbA1c value of 7.5%.10

**Measurements of clinical characteristics and body composition analysis**

Different parameters such as detailed history, BMI, WHR (waist-hip-ratio), pulse and blood pressure (BP) was recorded. Body composition of all participants was analyzed by bioelectrical impedance analysis (BIA) using commercially available Body Composition Analyzer (Type BC-418 MA, TANITA Corporation Japan).11 The bioimpedance analyzer uses eight points of tactile electrodes for making the recordings (contact at the hands and feet). This technique uses multiple frequencies to measure total body water, fats and fat free mass in total and its segmental distribution in trunk and limbs.

**Serum Assays**

Venous blood samples were collected from all subjects in fasting state of 10-12 hours. Serum was separated by centrifugation at 1500 was separated

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**TABLE I: COMPARISON OF CLINICAL CHARACTERISTICS BETWEEN CONTROL AND DIABETIC PATIENTS (MALE 39 AND FEMALES 24)**

| Variables          | T2DM Mean±SD (Range) | Control Mean±SD (Range) | Significance p Value |
|--------------------|----------------------|-------------------------|----------------------|
| Male/Females       | 19/11                | 20/13                   |                      |
| Age (years)        | 54.84±9.28 (25-67)   | 49.38±13.58 (30-80)     | 0.063                |
| Pulse (bpm)        | 80.93±15.21 (57-117) | 78.48±12.71 (56-108)    | 0.314                |
| WHR                | 0.94±0.06 (1.63-1.6) | 0.89±0.07 (1.00-1.10)   | 0.447                |
| SBP (mm Hg)        | 142.33±20.27 (101-186) | 119.07±16.43 (92-156)   | 0.545                |
| DBP (mm Hg)        | 85.53±8.83 (73-111)  | 79.47±14.75 (40-107)    | 0.042                |
| FBG (mmol/L)       | 9.29±3.06 (4.40-15.19) | 4.75±0.61 (3.80-5.81)   | 0.001                |
| HbA1C (%)          | 8.26±1.35 (5.70-10.80) | 5.14±0.45 (4.90-5.21)   | 0.009                |
| Visfatin (ng/ml)   | 7.01±3.79 (2.23-15.19) | 4.02±2.74 (1.28-12.00)  | 0.001                |

Values are compared by Student’s t test. T2DM (Type 2 diabetes mellitus), WHR (Waist-hip ratio), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), FBG (Fasting blood glucose), HbA1C (Glycosylated hemoglobin). BMI (Body mass index), BF% (Body fat percentage), BFM (Body fat mass), FFM (Fat free mass), TFM (Truncal fat mass), TF (Truncal fat), VF (Visceral fat).

**TABLE II: COMPARISON OF BODY COMPOSITION INDICES BETWEEN CONTROL AND DIABETIC PATIENTS**

| Analytes      | T2DM Mean±SD (Range) | Control Mean±SD (Range) | Significance p Value |
|---------------|----------------------|-------------------------|----------------------|
| Male/Females  | 19/11                | 20/13                   |                      |
| BMI (kg/m²)   | 33.27±5.81 (22.50-46.40) | 31.39±7.00 (22.7-40.12) | 0.692                |
| BF%           | 38.96±7.85 (24-52)   | 34.63±8.69 (20-49)      | 0.353                |
| BFM (kg)      | 35.01±11.24 (20.20-71.60) | 31.19±13.18 (13.70-79.40) | 0.566                |
| FFM (kg)      | 49.28±11.21 (13.70-74.80) | 49.63±8.66 (37.50-72.31) | 0.499                |
| VF scores     | 10.03±5.95 (8.00-10.03) | 5.44±4.71 (5-14)        | 0.005                |
| TF (kg)       | 38.04±5.70 (26-50)   | 35.18±6.31 (26-46)      | 0.480                |
| TFM (kg)      | 17.78±5.40 (9.10-17.78) | 14.67±6.41 (16.21-32.80) | 0.428                |

Values are compared by Student’s t test. BMI (Body mass index), BF% (Body fat percentage), BFM (Body fat mass), FFM (Fat free mass), VF (Visceral fat), TF (Truncal fat), TFM (Truncal fat mass).
Statistical analysis

Data was analyzed using SPSS (Version 21.0). All numerical data were expressed as mean and standard deviation (SD). Student’s t test was used for normally distributed data and Mann-Whitney U test for data which was not following normal distribution. Spearman’s rank order and Pearson correlations were used where needed.

RESULTS

This study assessed the correlation between serum visfatin, glycemic control (via HbA1c) and body composition in T2DM subjects. The mean age of the T2DM patients was 54.84±9.28 years compared to 49.38±13.58 of the healthy controls.

Comparison of the anthropometric and clinical characteristics between T2DM and healthy subjects showed no significant differences in age, pulse, waist, hip, WHR, systolic BP, weight and height (Table I). Serum visfatin levels were 7.01±3.79 ng/ml in subjects with T2DM and 4.02±2.74 ng/ml in healthy subjects (p=0.046). However, diastolic BP, FBS, and HBA1c were significantly higher in diabetics versus healthy subjects. Body composition indices such as BMI, BMR, fat mass, fat percentage, truncal fat and truncal fat mass differences were not significantly different between T2DM and control groups (Table II). Furthermore, Serum visfatin levels were 9.29±3.44 ng/ml in T2DM with poor glycemic control (HbA1c >7.5%) as compared to 4.24±1.87 ng/ml in diabetic patients with good glycemic control (HbA1c <7.5%) [p=0.001]. (Figure 1). Visfatin correlated positively with BMI (r=0.284, p<0.05), BF% (r=0.302, p<0.05), BFM (r=0.280, p<0.05), visceral fat (r=0.263, p<0.05) and HbA1c (r=0.394, p<0.01) (Table III). 

DISCUSSION

This study was an effort to measure and assess serum visfatin levels and its relationship with glycemic control and body composition in patients with T2DM compared with a group of healthy control subjects. Our study showed positive correlation of serum visfatin with body adiposity and glycemic control. Serum visfatin levels are also found to be positively correlated with increasing the severity of coronary artery disease in patients having a high SYNTAX scoring which is a unique tool to score complexity of coronary artery disease. Furthermore, it can serve as a useful biomarker in predicting high SYNTAX scores in angina pectoris patients for coronary artery bypass grafting. Visfatin is reported to be associated with insulin resistance and exhibits proinflammatory properties.

It is also known that insulin resistance and inflammation are one of the main contributors in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), however, the exact relationship between the role of visfatin in NAFLD development remains uncertain. The positive correlation found in our study with body adiposity provides an evidence that high levels may also be involved in the pathogenesis of fatty liver disease, and needs to be further explored. Irisin and visfatin in diabetic nephropathy patients are found to be significantly raised in comparison to T2DM without nephropathy. Furthermore, the levels were raised with the severity of nephropathy staging, suggesting the index of severity in diabetic nephropathy. Irisin is a myokine that is usually released from the muscle immediately after exercise. It is secreted from fibronectin type III domain containing 5 (FNDC5) after the cleavage of its extracellular portion. Zhang M, et al. reported the irisin is a significant marker for macrovascular disease in T2DM. Ebert T, et al. reported that irisin levels were decreased in the advanced stage of the chronic kidney disease and could be used as a marker to assess the renal function.

Serum visfatin plays significant role in numerous physiological and pathological
The results of this study show that T2DM patients have high visfatin levels which are significantly higher in T2DM patients with poor glycemic control compared to good glycemic control. Moreover, visfatin levels are positively associated with body adiposity indices including visceral fat.

**RECOMMENDATIONS**

Long-term prospective trials on larger scale are needed in diabetic patients to explore the true links between T2DM and adipokines.

**ACKNOWLEDGMENTS**

We would also like to Mr. Timhar Amlih for his cooperation and assistance.

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**TABLE III: SPEARMAN’S CORRELATION BETWEEN SERUM VISFATIN, BODY COMPOSITION AND GLYCEMIC CONTROL**

| AGE | WHR | SBP | DBP | BMI | BF% | BFM | VF | HbA1C | Visfatin |
|-----|-----|-----|-----|-----|-----|-----|----|-------|---------|
| AGE | 1.000 |     |     |     |     |     |    |       |         |
| WHR | 0.184 | 1.000 |     |     |     |     |    |       |         |
| SBP | 0.592** | 0.272 | 1.000 |     |     |     |    |       |         |
| DBP | 0.130 | 0.361* | 0.544** | 1.000 |     |     |    |       |         |
| BMI | -0.101 | 0.090 | -0.004 | -0.023 | 1.000 |     |    |       |         |
| BF% | -0.007 | 0.197 | 0.054 | 0.034 | 0.759*** | 1.000 |     |       |         |
| BFM | -0.095 | 0.170 | -0.046 | -0.031 | 0.923*** | 0.872** | 1.000 |     |         |
| VF | 0.083 | 0.241 | 0.126 | 0.104 | 0.585** | 0.684** | 0.636** | 1.000 |     |
| HbA1c | 0.404** | 0.357* | 0.548** | 0.204 | 0.406** | 0.423** | 0.383** | 0.490** | 1.000 |
| Visfatin | 0.135 | 0.118 | 0.173 | 0.123 | 0.284* | 0.302* | 0.280* | 0.263* | 0.394** |

*p<0.05, **p<0.01; WHR (Waist-hip-ratio), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), BMI (Body mass index), BF% (Body fat percentage), BFM (Body fat mass), VF (Visceral fat), HbA1c (Glycosylated hemoglobin).
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The manuscript-based abstract was published as part of special issue: “Abstracts of the 31st International Congress of Clinical Neurophysiology (ICCN) of the IFCN, May 1 - 6, 2018, Washington, DC, USA”. Available from URL: https://www.sciencedirect.com/science/article/pii/S1388245718307272. DOI: 10.1016/j.clinph.2018.04.428.

AUTHORS’ CONTRIBUTIONS
Following authors have made substantial contributions to the manuscript as under:

SSH: Conception and study design; acquisition, analysis and interpretation of data, drafting the manuscript, approval of final version to be published

SB: Acquisition of data, drafting the manuscript, critical review, approval of final version to be published

SHH: Analysis and interpretation of data, drafting the manuscript, critical review, approval of final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST
Authors declared no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE
Work on this study was supported by Deanship of Scientific Research (Grant Number: RGP-1438-048) King Saud University, Riyadh, Saudi Arabia

DATA SHARING STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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KMUJ 2020, Vol. 12 No. 4