The relation between plasma levels of nesfatin-1 and different grades of diabetic kidney disease in patients with type 2 diabetes
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Introduction
Nesfatin-1 is an 82 amino-acid length polypeptide derived from calcium and DNA-binding protein NUCB2 [1]. The nesfatin-1 is prominently expressed in several regions of the hypothalamus nuclei. Moreover, it is expressed in several peripheral tissues including pancreatic β cells. Plasma levels of nesfatin-1 are reduced by fasting, and increased after refeeding, and this suggests that nesfatin-1 plays a role in satiety regulation and, possibly, energy homeostasis [2].

Background
Diabetic kidney disease (DKD) is the leading cause of renal failure. Diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. Nesfatin-1 is an anorectic polypeptide with potent metabolic regulatory effects and its circulating levels are shown to be elevated in type 2 diabetes mellitus (T2 DM). Nesfatin-1 may be involved in the pathogenesis of DKD through inflammatory mechanisms.

The aim of the work was to study the relation between plasma nesfatin-1 levels and different grades of DKD in patients with T2 DM.

Patients and methods
This study was conducted on 120 patients with T2 DM and 20 controls selected from the inpatient department and outpatient clinics of the Internal Medicine Department in Menoufia University Hospital. The selected individuals were grouped into four groups: group 1 included 20 healthy individuals, group 2 included 40 patients with T2 DM with normoalbuminuria, group 3 included 40 patients with T2 DM with microalbuminuria, and group 4 included 40 patients with T2 DM with macroalbuminuria.

Members of the study were subjected to thorough history with special emphasis on age, sex, and duration of the DM. Investigations included fasting blood glucose, glycosylated hemoglobin, complete urine analysis, serum creatinine, urine albumin–creatinine ratio, estimated glomerular filtration rate, and plasma nesfatin-1.

Results
Plasma nesfatin-1 was significantly higher in group 4 compared with other groups, in group 3 compared with groups 1 and 2, and in group 2 compared with group 1. There was a positive significant correlation between plasma nesfatin-1 and serum creatinine, urine albumin–creatinine ratio, and glycosylated hemoglobin and negative significant correlation between plasma nesfatin-1 and estimated glomerular filtration rate in the studied diabetic patients. There was no correlation between plasma nesfatin-1 and BMI and duration of diabetes in the diabetic patients.

Conclusion
From this study, we can conclude that plasma nesfatin-1 is significantly higher in patients with DKD, and there is a positive correlation between plasma nesfatin-1 level and the grades of DKD. So, plasma nesfatin-1 may be considered for prediction of developing DKD in a previously unaffected patients with DM.

Keywords: diabetic kidney disease, plasma nesfatin-1, type 2 diabetes mellitus

Nesfatin-1 crosses the blood–brain barrier in both the blood-to-brain and brain-to-blood directions by nonsaturable mechanisms [3].

A research study has shown an antihyperglycemic effect of nesfatin-1. The results obtained indicate...
that the antihyperglycemic effect of nesfatin-1 is peripheral and dependent on time, dose, and insulin.

Experimental studies have also linked nesfatin-1 to enhanced hepatic and peripheral insulin sensitivity by promoting peripheral glucose uptake and decreasing gluconeogenesis through different mechanisms [4,5].

Nesfatin-1 has been studied in several metabolic dysregulations such as obesity, inflammation, and diabetes [6,7].

Diabetic kidney disease (DKD) is a chronic microvascular complication of diabetes that may lead to end-stage renal disease [8]. Early diagnosis and effective treatment of DKD may delay the progression of this disease [9]. So, reliable screening biomarker of DKD would be of value and an important issue in detecting the patients in need for further assessment and treatment. We presumed that nesfatin-1 may play a role in the development of DKD.

The aim of the work was to study the relation between plasma nesfatin-1 levels and different grades of DKD in type 2 diabetes mellitus (T2 DM).

Patients and methods
This study was conducted on 120 patients with T2 DM selected from the inpatient department and outpatient clinics of the Internal Medicine Department during the period from June 2017 to November 2017. There were 40 patients with normoalbuminuria and 80 patients with DKD. DKD was confirmed by exclusion of the other conditions that may affect the kidneys through full history and clinical examination to exclude uncontrolled hypertension, chronic inflammatory disease, malignancy, acute infections, and nephropathy owing to causes other than diabetes.

After taking their consent for participation in the study, all members of the study were subjected to thorough history with special emphasis on age, sex, duration of DM, and complete physical examination. Investigations included fasting blood glucose, glycosylated hemoglobin, fasting serum insulin, serum creatinine, serum alanine transaminase, urine analysis, urine albumin–creatinine ratio, and plasma nesfatin-1 concentration were measured using human enzyme-linked immunosorbent assay kits, human nesfatin-1 PicoKine ELISA Kit (Boster Biological Technology, Pleasanton, California, USA). Glomerular filtration rate was estimated by Cockcroft–Gault formula [10].

Assessment of insulin resistance was done by using homeostasis model assessment 2 (HOMA2) calculator according to the updated computer-based HOMA2 model in patients with normal and impaired glucose tolerance [11].

Statistical methodology
Data were analyzed using IBM SPSS software package, version 20.0 (Armonk, NY: IBM Crop Chicago, USA).

Qualitative data were presented as frequency and percentage. Quantitative data were presented as mean and SD. To compare between groups, we used \( \chi^2 \)-test, analysis of variance test, and least significant difference and correlation coefficient. Significance level value was \( P \) equal to or less than 0.05.

Results
There was no significant difference between the studied groups regarding age and sex. BMI was significantly higher in diabetic groups compared with the control group. The duration of DM was significantly higher in group 4 compared with groups 2 and 3.
Glycosylated hemoglobin was significantly higher in group 4 compared with other diabetic groups. Urine albumin–creatinine ratio (UACR) was significantly higher in group 4 compared with other groups and in group 3 compared with groups 2 and 1. The estimated glomerular filtration rate (eGFR) was significantly lower in group 4 compared with other groups and in group 3 compared with groups 1 and 2 (Table 1).

Plasma nesfatin-1 level was significantly higher in diabetic groups compared with control group and in group 4 compared with other groups and in group 3 compared with groups 1 and 2, and in group 2 compared with group 1 (Table 2).

There was a positive significant correlation between plasma nesfatin-1 and serum creatinine, glycosylated hemoglobin (HbA1c), and UACR, and a negative significant correlation between plasma nesfatin-1 and eGFR in the diabetic patients. There was no correlation between plasma nesfatin-1 and BMI and duration of diabetes (Table 3).

**Discussion**

The pathogenesis of DKD is multifactorial. Therefore, to study the relation between nesfatin-1 and DKD, we study also its relation to BMI, duration of diabetes, glycemic control, and insulin resistance.

In the current study, plasma nesfatin-1 was significantly higher in diabetic patients compared with the nondiabetic individuals; moreover, it is significantly higher in macroalbuminuric than microalbuminuric and normoalbuminuric patients.

There was a positive correlation between the nesfatin-1 and serum creatinine and UACR, whereas there was a negative correlation between nesfatin-1 and eGFR.

Although plasma nesfatin-1 was shown to be increased in patients with diabetes [12], conflicting results have refuted the presence of such association [13].

Possible inflammatory mechanisms should be considered to explain the serum nesfatin-1 increased levels in patient with DKD. Albuminuria actively contributes to endothelial dysfunction that is predominantly characterized by long-term and low-grade state of systemic inflammation. At the level of hypothalamus and brain stem, a proportion of nesfatin-1-producing neurons are highly sensitive to peripheral inflammatory stimuli [14,15].

Elevated plasma nesfatin-1 is also because of activation of mechanisms against DKD-mediated metabolic and inflammatory disturbance. Consistently, Joing et al. [14] demonstrated the potency of nesfatin-1 as a potential therapeutic agent in renal ischemic reperfusion injury through its anti-inflammatory, antioxidant, and antiapoptotic effect. Nesfatin-1 has also an anti-inflammatory feature, especially in brain damage [15,16].

Recent histopathologic studies reported the overexpression levels of N4CB2 nesfatin-1 and binding sites localized to the renal tissue cells at both mRNA and protein levels in the absence of inflammation. These reports [17] suggest that the increase in plasma NUCB2 nesfatin-1 is derived from the renal tubules in DKD that acts as one of renal protective mechanisms [18].

**Table 1** Comparison between the studied groups according to demographic and laboratory investigations

<table>
<thead>
<tr>
<th></th>
<th>G1 (n=20)</th>
<th>G2 (n=40)</th>
<th>G3 (n=40)</th>
<th>G4 (n=40)</th>
<th>F-test</th>
<th>P</th>
<th>LSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.0±7.6</td>
<td>54.6±8.1</td>
<td>53.9±6.1</td>
<td>55.5±7.1</td>
<td>0.342</td>
<td>0.795</td>
<td>–</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>6.1±1.7</td>
<td>7.3±2.3</td>
<td>10.1±2.1</td>
<td>21.732</td>
<td>&lt;0.001*</td>
<td>2 vs. 3.4 3 vs. 4</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0±4.128</td>
<td>27.18±2.01</td>
<td>29.28±3.54</td>
<td>31.19±4.02</td>
<td>14.443</td>
<td>&lt;0.001*</td>
<td>2 vs. 3.4 3 vs. 4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.51±0.29</td>
<td>6.9±0.9</td>
<td>6.7±6.0</td>
<td>10.04±7.21</td>
<td>22.962</td>
<td>&lt;0.001*</td>
<td>2 vs. 3.4 3 vs. 4</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.66±0.12</td>
<td>1.06±0.17</td>
<td>1.5±0.18</td>
<td>2.4±0.65</td>
<td>128.451</td>
<td>&lt;0.001*</td>
<td>1 vs. 3.4 2 vs. 3.4 3 vs. 4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.20±3.6</td>
<td>209.7±31.06</td>
<td>1201±206.5</td>
<td>1106.443</td>
<td>&lt;0.001*</td>
<td>2 vs. 3.4 3 vs. 4</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>114.4±7.6</td>
<td>97.6±5.6</td>
<td>77.6±6.4</td>
<td>41.3±5.7</td>
<td>837.219</td>
<td>&lt;0.001*</td>
<td>1 vs. 3.4 2 vs. 3.4 3 vs. 4</td>
</tr>
</tbody>
</table>

*Statistically significant at P≤0.05.

eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model assessment for insulin resistance; LSD, least significant difference; UACR, urine albumin–creatinine ratio; *Statistically significant at P≤0.05.

**Table 2** Comparison between the studied groups regarding plasma nesfatin-1 levels

<table>
<thead>
<tr>
<th></th>
<th>G1 (n=20)</th>
<th>G2 (n=40)</th>
<th>G3 (n=40)</th>
<th>G4 (n=40)</th>
<th>F-test</th>
<th>P</th>
<th>LSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma nesfatin-1 levels (pg/ml)</td>
<td>0.41±0.94</td>
<td>2.03±1.01</td>
<td>3.04±1.99</td>
<td>4.88±2.04</td>
<td>41.894</td>
<td>&lt;0.001*</td>
<td>1 vs. 3.4 2 vs. 3.4 3 vs. 4</td>
</tr>
</tbody>
</table>

*Statistically significant at P≤0.05.
Table 3 Correlation between the plasma nesfatin-1 and other parameters in the diabetic patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum nesfatin-1</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes</td>
<td>0.135</td>
<td>0.141</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.640</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Urine albumin-creatinine ratio</td>
<td>0.511</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>−0.607</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>0.576</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.154</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td>Homeostasis model assessment of insulin resistance</td>
<td>0.68</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

r, correlation coefficient; *Statistically significant at P≤0.05.

In our study, there was a positive correlation between nesfatin-1 and homeostasis model assessment of insulin resistance, which is in agreement with Zhang et al. [12]. They confirmed a positive correlation between nesfatin-1 with fasting plasma insulin and HOMA. Moreover, there was a positive correlation between nesfatin-1 and HbA1c, which is in agreement with Ademoglu et al. [19], who found plasma nesfatin-1 to be positively associated with HbA1c. Other groups found nesfatin-1 and HbA1c were negatively correlated in hypothyroid patients [20]. Increased level of HbA1c and poor glycemic control act as an inflammatory milieu in the kidney and stimulate protein kinase-c and oxidative stress, which increases the expression of cytokines with more attraction of inflammatory cells to the kidney, which in turn lead to endothelial dysfunction and albuminuria.

Conclusion

Plasma nesfatin-1 levels are significantly elevated in patients with T2 DM and DKD, and such levels of elevation are related to the severity of DKD. Owing to the highly significant statistical difference in plasma nesfatin-1 levels between diabetes with normoalbuminuria and diabetics with albuminuria, it has been known that some of patients with DKD are normoalbuminuric, so plasma nesfatin-1 level can add a predictive value in diagnosis of DKD in previously unaffected patients with diabetes.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
11. The University of Oxford. HOMA calculator; 2016. Available at: https://www.dtu.ox.ac.uk/homacalculator/. [Accessed 8 October 2016]