Serum Nesfatin-1 Levels in Patients With Different Glucose Tolerance Levels

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Summary

The aim of this study was to compare the levels of nesfatin-1 in healthy subjects with those in prediabetic and diabetic patients who have different glucose tolerance levels. Overall, 100 subjects were divided into 5 groups healthy control (C), impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), metabolic syndrome (MS) and type 2 diabetes mellitus, (Type 2 DM). Glycated hemoglobin (HbA1c) assessed the glycemic control. Homeostasis model assessment of insulin resistance (HOMA-IR) was determined using computer analyses. Nesfatin-1 levels were measured using ELISA method. IFG and IGT (prediabetic groups) from MS and Type 2 DM (diabetic groups) differed significantly in HOMA-IR. The nesfatin-1 levels were lower, although not statistically significant, in IFG (0.937 ± 0.03 ng/ml, $p=0.07$) and IGT (1.039 ± 0.06 ng/ml, $p=0.5$) groups compared to healthy subjects (1.094 ± 0.07 ng/ml). However, the nesfatin-1 levels were lower in patients with Type 2 DM (0.867 ± 0.02 ng/ml, $p=0.007$) and MS (0.885 ± 0.01 ng/ml, $p=0.01$) compared to healthy subjects. Nesfatin-1 levels were significantly lower in diabetic patients compared to healthy subjects. This study supports the role of insulin resistance in decreased nesfatin-1 levels in patients with Type 2 DM and MS.

Key words

Type 2 diabetes mellitus • Impaired glucose regulation • Nesfatin-1 • Insulin

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Introduction

It is well known that nesfatin-1 has important effects on food intake (anorexigenic effects) and regulation of energy homeostasis through mechanism(s) independent of leptin (Oh-I *et al.* 2006, Kohno *et al.* 2008, Stengel and Taché 2014). Recent data has also revealed regulatory role of nesfatin-1 in glucose homeostasis which is antihyperglycemic (Su *et al.* 2010, Nakata *et al.* 2011). The detection of nesfatin-1 located in beta cell containing insulin could provide an evidence of its connection with glucose metabolism (Stengel *et al.* 2009, Goebel *et al.* 2009, Foo *et al.* 2010).

However, the mechanism of action through which nesfatin-1 regulates glucose metabolism is not clear yet. Type 2 diabetes mellitus (Type 2 DM) is typically associated with an altered glucose metabolism, insulin resistance, abnormal fasting glucose levels, and impaired glucose tolerance. In addition, prediabetes (impaired glucose regulation), which World Health Organisation defines as impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT), also serious impairs glucose metabolism (Waugh *et al.* 2007). The studies in literature on the relationships between diabetes and nesfatin-1 have revealed conflicting results. Some studies have shown a low nesfatin-1 levels in patient with Type 2 DM and high nesfatin-1 levels in patients with Type 1 DM (Li *et al.* 2010). However, the other studies have observed high nesfatin-1 levels in patients with Type 2 DM and patients with IGT (Zhang *et al.* 2012).

To our knowledge, no extensive studies have

been conducted in patients with different glucose metabolic impairment and nesfatin-1 levels. It is important to understand whether nesfatin-1 can be used as a supportive tool in the diagnosis and treatment of glucose metabolic impairments.

In the present study, we comparatively examined the nesfatin-1 levels in patients with IFG, IGT, Type 2 DM, metabolic syndrome (MS) and healthy subjects.

Materials and Methods

Subjects

This study included 100 participants: 80 patients (38 males; 42 females) with different impaired glucose tolerance (who attended Diabetes, Endocrine, and Metabolism Unit at Firat University Hospital) and 20 healthy subjects.

The subjects were divided into 5 different groups: 20 healthy subjects comprised the control group (C group 1, age 39.2 ± 1.2 years, height 168 ± 1 cm, weight 68.0 ± 2.2 kg, body mass index (BMI) 24.1 ± 0.7 kg/m²), 20 patients with impaired fasting glycemia (IFG group 2, age 42.3 ± 1.2 years, height 162 ± 2 cm, weight 81.7 ± 5.1 kg, BMI 31.1 ± 2.1 kg/m²), 20 patients with impaired glucose tolerance (IGT group 3: age 41.8 ± 1.3 years, height 163 ± 2 cm, weight 75.8 ± 4.2 kg, BMI 28.6 ± 1.6 kg/m²), 20 patients with metabolic syndrome (MS group 4, age 38.5 ± 1.4 years, height 166 ± 1 cm, weight 84.3 ± 3.1 kg, BMI 30.7 ± 1.4 kg/m²), and 20 patients with type 2 diabetes mellitus (Type 2 DM group 5, age 40.6 ± 1.4 years, height 164 ± 2 cm, weight 79.4 ± 2.3 kg, BMI 29.6 ± 0.8 kg/m²).

The diagnoses of Type 2 DM, IFG, and IGT were made according to the American Diabetes Association criteria. IFG is defined by the fasting glucose level ≥ 100 and < 126 mg/dl (Genuth *et al.* 2003). IGT is defined by an elevated 2-h glucose level ≥ 140 and < 200 mg/dl after a 75-g glucose load on the oral glucose tolerance test in the presence of a fasting glucose level < 126 mg/dl (Genuth *et al.* 2003). MS was identified using the Adult Treatment Panel III report (ATP III) and the group MS included only patients with Type 2 DM (Grundy *et al.* 2004).

Before participating in the study, all patients and control subjects underwent physical examination and laboratory evaluation including lipid parameters, thyroid function tests, and serum cortisol measurement for probable endocrine pathology (Liu *et al.* 2014).

The subjects in control group had a normal

glucose tolerance (no diabetes history, endocrine disorders, and any medications). Clinical exclusion criteria included Type 1 DM, gestational DM, pregnancy, hormone replacement therapy, major depressive disorders and cancer, a history of drug use (systemic glucocorticoids and antipsychotics), thyroid and other endocrine disorders, severe acute or chronic infectious disease, systemic diseases (heart failure, liver or kidney disease, or lung disease).

All procedures were conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The Firat University Local Ethic Committee approved the study protocol, and informed written consent was obtained from each subject before the study.

Biochemical parameters and hormone analyses

Blood samples (5 ml) were drawn from a forearm vein in the morning after overnight fasting for hormone and other biochemical analyses. All samples were placed into aprotinin or EDTA containing tubes until centrifugation at 4500 rpm for 5 min at 4 °C. The separated serum and plasma were stored at -80 °C and analyzed immediately at the end of study (Hettich, Zentrifugen Universal 32 R, Germany). Samples from each subject were analyzed in the same assay.

Fasting serum nesfatin-1 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Belmont, CA, USA). The linear range of the assay was 0.78 ng/ml. The inter-assay and the intra-assay coefficients of variation were 10 % and 15 %, respectively.

Plasma insulin level was measured according to the electrochemiluminescence immunoassay method using an automated immunoassay analyzer (Immulite 2500 Insulin, Diagnostic Products Corporation, Los Angeles, CA, USA). Serum glucose, total cholesterol, very low density lipoprotein (VLDL), high density lipoprotein (HDL), and low density lipoprotein (LDL) cholesterol levels were determined using commercial kits in Olympus AU600 autoanalyzer.

The glycemic control of the patients was assessed by glycated hemoglobin (HbA1c) (i.e. the mean plasma glucose level over the preceding 2 to 3 months). HbA1c levels were detected by autoanalyzer from EDTA containing blood samples. Homeostasis model assessment of insulin resistance (HOMA-IR) was determined using computer analyses (i.e. fasting blood glucose and insulin levels).

Statistical analyses

Power analysis was used to determine the number of subjects in each group. Values are expressed mean $\pm$ standard error. The Kolmogorov-Smirnov Z test showed that the data were normally distributed and thus using parameters test was justified. One way ANOVA was used to determine between group differences, and Pearson correlation analysis was used to evaluate the relationship between observed values with $p < 0.05$ being accepted as significant statistically.

Results

The biochemical results among study groups are given in Table 1. No significant correlation was detected among the nesfatin-1 levels, lipid parameters (including, VLDL, LDL and HDL), and BMI in any of the study groups. The insulin levels were significantly higher in patients groups compared with the control group. In addition, insulin levels were significantly different in diabetic groups (MS and Type 2 DM) compared to prediabetic groups (IFG and IGT) ($p = 0.001$) (Table 1).

Table 1. The clinical characteristics of the study groups. Fasting blood glucose (BG_F), postprandial blood glucose (BG_{PB}), fasting insulin, low-density lipoprotein (LDL), very low density lipoprotein (VLDL) high-density lipoprotein (HDL).

	BG_F (mg/dl)	BG_{PB} (mg/dl)	Insulin (μ U/ml)	LDL (mg/dl)	VLDL (mg/dl)	HDL (mg/dl)
Control	91 $\pm$ 1	123 $\pm$ 2	4.86 $\pm$ 0.8	73 $\pm$ 3	18 $\pm$ 1	62 $\pm$ 2
IFG	111 $\pm$ 1*	128 $\pm$ 2*	7.00 $\pm$ 0.6*	110 $\pm$ 6*	29 $\pm$ 3*	45 $\pm$ 1*
IGT	116 $\pm$ 1*	186 $\pm$ 2*	7.74 $\pm$ 0.6*	133 $\pm$ 8*	38 $\pm$ 3*	48 $\pm$ 1*
MS	124 $\pm$ 5*	174 $\pm$ 8*	9.92 $\pm$ 0.9* $\ddagger$	120 $\pm$ 5*	48 $\pm$ 3*	39 $\pm$ 1*
Type 2 DM	234 $\pm$ 11*	321 $\pm$ 20*	10.14 $\pm$ 0.9* $\ddagger$	137 $\pm$ 4*	47 $\pm$ 5*	36 $\pm$ 1*

Values are presented as mean $\pm$ SEM. * indicates significant differences compared to the control ($p < 0.05$). $\ddagger$ indicates significant differences compared to the IFG and IGT ($p < 0.05$).

Fig. 1. Nesfatin-1 levels in response to the control (C), impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), metabolic syndrome (MS), and Type 2 DM groups. Values are presented as mean $\pm$ SE. * indicates significant differences compared to the control levels.

The serum nesfatin-1 levels in healthy subjects and patients with IFG, IGT, MS, and Type 2 DM are presented in Figure 1. The nesfatin-1 levels for control group were 1.094 $\pm$ 0.07 ng/ml. Although it was lower in patients with IFG (0.937 $\pm$ 0.03 ng/ml) and IGT

(1.039 $\pm$ 0.06 ng/ml), the differences in nesfatin-1 levels between control and two prediabetic groups were not significant ($p = 0.07$ and $p = 0.5$, respectively) (Fig. 1). However, we observed statistically significant lower nesfatin-1 levels in patients with Type 2 DM (0.867 $\pm$ 0.02 ng/ml) ($p = 0.007$) and MS (0.885 $\pm$ 0.01 ng/ml) ($p = 0.01$), compared to the control group (Fig. 1).

The HOMA-IR (units) (Fig. 2) and HbA1c (%) (Fig. 3) levels were significantly higher in patients with IFG (1.916 $\pm$ 0.19 units, $p < 0.0001$; 5.40 $\pm$ 0.11 %, $p < 0.0001$), IGT (2.164 $\pm$ 0.17 units, $p < 0.0001$; 6.37 $\pm$ 0.12 %, $p < 0.0001$), MS (3.084 $\pm$ 0.35 units, $p < 0.0001$; 5.90 $\pm$ 0.15 %, $p < 0.0001$) and Type 2 DM (6.694 $\pm$ 0.53 units, $p < 0.0001$; 9.11 $\pm$ 0.32 %, $p < 0.0001$) compared to the control group (1.057 $\pm$ 0.17 units; 4.87 $\pm$ 0.08 %), respectively. The HOMA-IR levels were significantly different between prediabetic (IFG and IGT) and diabetic (Type 2 DM and MS with Type 2 DM) groups: IGT vs. MS, $p = 0.02$; IGT vs. Type 2 DM, $p < 0.0001$; IFG vs. MS, $p = 0.006$; IFG vs. Type 2 DM, $p < 0.0001$. However, no significant differences were observed in HOMA-IR levels between IFG and IGT groups ($p = 0.3$).

Fig. 2. HOMA-IR in response to the control (C), impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), metabolic syndrome (MS), and Type 2 DM groups. Values are presented as mean $\pm$ SE. * indicates significant differences compared to the control levels.

Fig. 3. HbA1c in response to the control (C), impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), metabolic syndrome (MS), and Type 2 DM groups. Values are presented as mean $\pm$ SE. * indicates significant differences compared to the control levels.

Discussion

The results of previous studies revealed that nesfatin-1 is becoming a vitally important peptide hormone for obesity (by effect on body energy metabolism), diabetes (effect involving glucose metabolism) (Masuo 2014), and mental-depressive disorders (Algul *et al.* 2013). In the present study, we compared nesfatin-1 levels in prediabetic and diabetic patients, including four different impaired glucose metabolisms, as determined by HOMA-IR. We determined that nesfatin-1 levels were slightly but not significantly lower in patients with IFG and IGT (prediabetic patients) compared to healthy subjects

(Fig. 1). However, nesfatin-1 levels were significantly lower in patients with Type 2 DM and MS compared to healthy subjects. It is important to clarify the response of nesfatin-1 at different levels of impaired glucose metabolism.

The finding indicating low nesfatin-1 levels in Type 2 DM (Li *et al.* 2010, Liu *et al.* 2014) and MS (Aksu *et al.* 2015) is associated with the findings of some previous studies. However, our finding was not in agreement with previous findings that have shown elevated nesfatin-1 levels in patients with Type 2 DM (Zhang *et al.* 2012) and patients with IGT (Guo *et al.* 2013). HOMA-IR was found to be significantly higher in diabetic groups with highly impaired glucose metabolism compared to control. Interestingly, it has been suggested that low nesfatin-1 levels of diabetic patients could be one of the stimulating factors in diabetic hyperphagia (Li *et al.* 2010). Thus, nesfatin-1 has a reducing effects on food intake, i.e. it acts as a potential anorexigenic agent (Oh-I *et al.* 2006, Li *et al.* 2010).

Importantly, we have also found significant differences ($p < 0.05$) in insulin resistance between diabetic (MS and Type 2 DM), and prediabetic (IFG and IGT) groups, as determined by HOMA-IR. Thus, insulin resistance and impaired insulin secretion could possibly explain for the significantly lower nesfatin-1 levels in diabetic group (Taylor *et al.* 1994). Distribution of fat mass in patients with MS may be the reason for the high insulin resistance (Grundy 2006). Several observations have indicated that nesfatin-1 affects glucose metabolism by increasing insulin sensitivity (Gonzalez *et al.* 2011, Li *et al.* 2013). Different insulin resistance mechanisms are involved in IFG (predominantly hepatic insulin resistance and normal muscle insulin sensitivity) and IGT (slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance) (Abdul-Ghani *et al.* 2006). Insulin treatment or improvement of blood glucose might play a role in the changes in nesfatin-1 in diabetic patients (Gonzalez *et al.* 2009).

The relationships between nesfatin-1 with body weight and insulin resistance in obese subjects have been shown (Anwar *et al.* 2014). In the present study, we did not find any correlation between nesfatin-1 levels and body weight or insulin resistance in any of the study groups. We observed significantly low nesfatin-1 levels in Type 2 DM and MS group compared to control group. The results of previous studies revealed significantly higher levels of serum nesfatin-1 in obese individuals than in control subjects (Anwar *et al.* 2014). In addition,

low nesfatin-1 levels have been reported in patients with anorexia nervosa (Ogiso *et al.* 2011). A significantly positive correlation between BMI and nesfatin-1 levels in obese individuals has been shown (Ramanjaneya *et al.* 2010), although a negative correlation has also been reported in non-obese subjects (Tsuchiya *et al.* 2010). In contrary, patients with insulin resistance had statistically insignificant lower nesfatin-1 levels compared to obese children without insulin resistance (Abaci *et al.* 2013). A recent study has shown that the insulin producing beta cells colocalized prepronesfatin in the islets of both mice and rats, suggesting a potential role of prepronesfatin-derived peptides in insulin secretion and glucose metabolism (Gonzalez *et al.* 2009).

Our study was limited by its cross-sectional design and, a relatively small sample size; therefore it cannot prove a causal relationship between altered nesfatin-1 levels and the development of Type 2 DM. Other important point to be emphasized is that all patients were not newly diagnosed, and some of them had already been getting therapy. Baseline characteristics of prediabetic, diabetic and control groups were not comparable, which may have had an effect on the

conclusion. Future studies concerning the nesfatin-1 levels in response to the diabetic therapy, including the effects of oral antidiabetic and insulin treatment, is needed. Establishing the biochemical and physiological effects of nesfatin-1 on the regulatory mechanisms of body energy systems will contribute to clarify the factors that might contribute to glucose metabolism impairment.

Conclusion

The novelty of our study is that we showed, for the first time, significantly lower nesfatin-1 levels in diabetic patients (Type 2 DM and MS) but not in prediabetic patients (IGT and IFG). Nesfatin-1 is a newly identified polypeptide probably involved, *inter alia*, in the regulation of food intake. It is important to clarify the relationships between nesfatin-1 and insulin resistance with regard to diabetes. To elucidate its physiological role further studies are required.

Conflict of Interest

There is no conflict of interest.

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