Association of serum Sestrin-2 level with insulin resistance, metabolic syndrome, and diabetic nephropathy in patients with type 2 diabetes

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Received 22 September 2018
Accepted 23 October 2018

The Egyptian Journal of Internal Medicine
2019, 31:107–114

Background
The aim of the study was to evaluate the relationship between serum Sestrin2, Insulin resistance (IR), metabolic syndrome (MetS), and diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (T2DM).

Patients and methods
The study group consisted of 155 patients with T2DM who were recruited and evaluated for DN. IR was evaluated by the homeostasis model assessment-insulin resistance (HOMA-IR). Sestrin2 levels were determined by enzyme-linked immunosorbent assay.

Results
Serum Sestrin2 levels showed significant positive correlations with tumor necrosis factor-α (r=0.247, P=0.018), triglycerides (r=0.178, P=0.021), total cholesterol (r=0.33, P=0.007), fasting c-peptide (r=0.164, P=0.035), and systolic blood pressure (r=0.171, P=0.041). A significant negative correlation was found between Sestrin2 levels and serum adiponectin (r=0.247, P=0.018). Also, Sestrin2 levels were positively correlated HOMA-IR (r=0.188, P=0.026). There was a progressive significant increase of mean HOMA-IR through Sestrin2 tertiles (P=0.001). A significant increase of mean serum Sestrin2 levels was found in relation to the presence of DN or MetS.

Conclusion
Serum Sestrin2 levels are significantly associated with IR, MetS, and DN in patients with T2DM.

Keywords:
diabetic nephropathy, insulin resistance, metabolic syndrome, Sestrin2, type 2 diabetes mellitus

Egypt J Intern Med 31:107–114
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1110-7782

Introduction

Diabetic nephropathy (DN) is a microvascular complication of diabetes which leads to end-stage renal disease worldwide [1,2]. The pathogenesis of DN may be caused by the contribution of adipokines and insulin resistance (IR) to induce inflammatory processes and modulate vascular function [3]. Metabolic syndrome (MetS), hyperglycemia, IR and hyperlipidemia associated with obesity are mainly caused by inflammation [4]. Renal impairment was found to be present before the occurrence of diabetes mellitus in groups of patients with MetS [5]. Adipose tissue synthesizes adiponectin which is correlated with obesity, type 2 diabetes mellitus (T2DM) [6], IR and their low levels are regarded as a risk factor for the development of MetS [7]. Sestrins are proteins that are induced by various stresses. Nutritional, genotoxic, oxidative stress and other environmental factors induce upregulation of Sestrin expression. Stress-responsive genes in mammals include Sestrins1, Sestrins2 and Sestrins3, whereas mammalian Sestrins1 and Sestrins2 are regulated by p53 [8]. A study by Lee *et al.* [9] showed upregulation of Sestrin2 in various tissues of a mice model of obesity and T2DM. In addition, Sestrin2 can increase fatty acid oxidation and lipolysis through the activation of adenosine monophosphate-activated protein kinase- mediated PPARa and mammalian target of rapamycin (mTOR) [10,11]. Insulin is an important regulator enhancing anabolism by stimulating mTOR and some studies mention that Sestrins could cross-talk with insulin signaling [10]. Although Sestrin2 has important roles in metabolic homeostasis, the associations of circulating Sestrin2 levels with DN in type 2 diabetic patients have not been investigated to date. Therefore, this study was designed to evaluate the association of Sestrin2 levels and DN in type 2 diabetic patients and their correlation with IR and MetS.

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Patients and methods

We recruited 155 T2DM patients. There were 80 male and 75 female patients with a mean age of 51.3 years, who were examined at the diabetes clinic of Zagazig University Hospital. We reviewed clinical and treatment history, biochemical and demographic data. The participants were classified as being a smoker (current or former) or nonsmoker. The study was performed in accordance with the principle of the Helsinki Declaration. Signed informed consent was obtained from all participants included in the study.

Measurement of serum Sestrin2 and other biochemical variables

Morning blood samples were obtained after an overnight fast. The serum was separated by centrifugation and then stored at −70°C until the assays were performed. Serum Sestrin2 levels were determined by enzyme-linked immunosorbent assay kits (Cusabio Biotech, Wuhan, China). Tumor necrosis factor-α (TNF-α) was determined using a commercially available immunoassay kit (Quantikine HS Human TNF-α immunoassay kit; R&D Systems, Minneapolis, Minnesota, USA). Plasma adiponectin levels were analyzed using radioimmunoassay for human adiponectin (Linco Research Inc., St Charles, Missouri, USA). Serum c-peptide levels were measured by radioimmunoassay (Roche Diagnostics, Germany). Serum leptin levels were determined using radioimmunoassay (leptin RIA kit; Linco Research Inc.). High-sensitivity C-reactive protein (hsCRP) was quantified using an IMMAGE automatic immunoassay system (Beckman-Coulter, Fullerton, California, USA)

Diabetic nephropathy and metabolic syndrome

Diabetic nephropathy was diagnosed according to the presence of albuminuria, which was assessed by radioimmunoassay. The participants were defined according to their baseline albumin excretion rate: normoalbuminuria (albumin <20 μg/min) or urine albumin of less than 30 mg/g creatinine, microalbuminuria (albumin, 20–200 μg/min) or urine albumin of 30–300 mg/g creatinine and macroalbuminuria (albumin ≥200 μg/min) urine albumin of more than or equal to 300 mg/g creatinine. Patients with persistent macroalbuminuria or microalbuminuria were considered having DN. Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease study equation. Insulin resistance was assessed by means of the homeostasis model assessment-insulin resistance (HOMA-IR), which is the product of fasting insulin (mUI/ml) and fasting glycemia (mmol/l) divided by 22.5. Metabolic syndrome was diagnosed by NCEP-ATP III criteria modified for waist circumference as follows. three or more of the following: central obesity, waist circumference more than or equal to 90 cm (male), more than or equal to 80 cm (female); hypertriglyceridemia: triglyceride more than or equal to 150 mg/dl or specific treatment; low high-density lipoprotein cholesterol: less than 40 mg/dl (male) and less than 50 mg/dl (female) or specific treatment; blood pressure (BP): systolic BP more than or equal to 130 mmHg or diastolic BP more than or equal to 85 mmHg or specific treatment and fasting plasma glucose more than or equal to 100 mg/dl or specific treatment or previously diagnosed type 2 diabetes [12].

Statistical analysis

Statistical evaluation was done using the Statistical Package for the Social Sciences software (version 20; SPSS, Chicago, Illinois, USA). Data are shown as mean±SD, except for non-normally distributed variables, for which geometric mean and median are shown or as a number and percentage of participants n (%). Sestrin2, HOMA-IR, hsCRP, triglyceride, and TNF-α were transformed as a natural logarithm. Chi-squared test was used for comparison between categorical variables. Independent *t* test was used for the evaluation of the mean significant difference of Sestrin2 levels between patients with and without DN. Patients were classified into tertiles based on serum Sestrin2 levels. Mean differences between Sestrin2 tertile groups were evaluated with one-way analysis of variance. Student's *t* test was used to compare means of levels of Sestrin2 levels and other variables where appropriate. Spearman's correlation analysis was used to test for the correlation between serum Sestrin2 levels and other clinical parameters.

Results

Baseline characteristics for the study population

The baseline characteristics of the study population are summarized in Table 1.

The mean values for age and BMI were 51.3 years and 25.2 kg/m^2, respectively. The mean diabetic duration was 8.4 years. The mean levels of serum Sestrin2 were 0.7 ng/ml (0.28–4.7 ng/ml) with no significant difference between sexes. The prevalence of MetS and hypertension were 65.8 and 42.6%, respectively. Eighty-three patients were on angiotensin receptor blocker (ARB) or/and angiotensin-converting enzyme inhibitor (ACEI). Eighty-nine (57.4%) patients were treated with statin. The incidence of DN was 74 patients (47.7%).

Table 1 Demographic and biochemical characteristics of the study population

Age (years)	51.3±8.7
Duration of DM (year)	8.4±7.2
Men/women n(%)	96/59 (61.9/38.1)
Smoking n(%)	72 (46.4)
Systolic BP (mmHg)	129.5±15.9
Diastolic BP (mmHg)	88.1±7.9
BMI (kg/m^2)	25.2±4.3
FPG (mg/dl)	139 (69–381)
HbA1C (%)	8.2±2.1 (5.1–15.9)
eGFR (ml/min/1.73 m^2)	90.2±16.3
Total cholesterol (mg/dl)	165.4±33.5
Triglycerides (mg/dl)	132 (41–994)
HDL-C (mg/dl)	46.8±11.8
LDL-C (mg/dl)	95.4±27.2
Hypertension n(%)	66 (42.6)
Leptin (ng/ml)	4.62 (0.56–50.1)
hsCRP (mg/dl)	0.09 (0.06–1.45)
Urinary albumin (mg/g)	7.1 (0.4–138)
Creatinine (mg/dl)	1.2 (0.7–1.6)
DN n(%)	74 (47.7)
Adiponectin (ng/ml)	2370 (420–15 232)
Sestrin2 (ng/ml)	0.7 (0.28–4.7)
FCP (ng/ml)	2.5±1.3
TNF-α (pg/ml)	1.74 (0.89–33.63)
HOMA-IR	2.74 (0.07–27.81)
Metabolic syndrome	102(65.8)
Treatment n(%)	
No medication	38 (24.5)
OHA	97 (62.5)
Insulin	9 (5.8)
OHA+insulin	11 (7.1)
Statin	89 (57.4)
ACEI/ARB	83 (53.5)

Data are shown as *n* (%), median (minimum–maximum) or as mean±SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; DM, diabetes mellitus; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; FCP, fasting C-peptide; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; OHA, oral hypoglycemic agent; TNF-α, tumor necrosis factor-α.

Bivariate correlation between Sestrin2 and clinical and biochemical parameters

Bivariate correlation between Sestrin2 levels and clinical and biochemical parameters are shown in Table 2. Serum Sestrin2 levels showed significant positive correlations with TNF-α (r=0.247, P=0.018), leptin (r=0.31, P=0.042), hsCRP (r=0.156, P=0.042), HOMA-IR (r=0.188, P=0.026), c-peptide (r=0.164, P=0.035), triglycerides (r=0.178, P=0.021), total cholesterol (r=0.33, P=0.007), low-density lipoprotein cholesterol (r=0.172, P=0.043), systolic BP (r=0.171, P=0.041), and eGFR (r=0.132, P=0.039). Serum Sestrin2 levels were negatively correlated with serum adiponectin (r=–0.191, P=0.032).

Table 2 Correlation of serum Sestrin2 with clinical and biochemical parameters

Index	Sestrin2 *r*	*P* value
Age	0.132	0.182
BMI	0.089	0.232
Duration of DM	–0.041	0.643
Systolic BP	0.171	0.041
Diastolic BP	0.089	0.253
FPG	0.104	0.188
HbA1C	0.064	0.492
eGFR	0.132	0.039
Creatinine	–0.072	0.403
Total cholesterol	0.33	0.007
Triglycerides	0.178	0.021
HDL-C	0.074	0.456
LDL-C	0.172	0.043
hsCRP	0.156	0.042
FCP	0.164	0.035
HOMA-IR	0.188	0.026
TNF-α	0.247	0.018
Leptin	0.331	0.042
Adiponectin	–0.191	0.032

BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FCP, fasting C-peptide; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TNF-α, tumor necrosis factor-α.

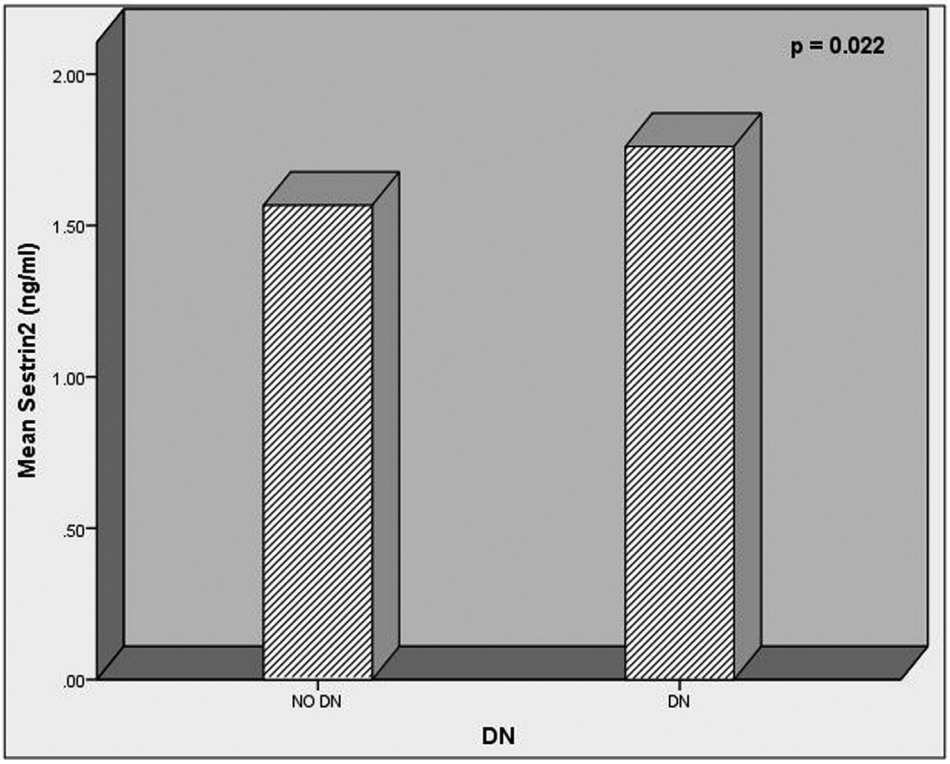
Statistical differences of the mean serum levels of Sestrin2 and other variables according to diabetic nephropathy status

The mean Sestrin2 serum levels were significantly different according to the presence or absence of DN (1.76±0.463 vs. 1.566±0.569 ng/ml, P=0.022) (Fig. 1). The patients were stratified into two groups according to whether or not they were treated with ARB or ACEI for DN and mean levels of Sestrin2 were compared between the two groups. There were no statistically significant differences in Sestrin2 levels between the two groups (DN not treated with ARB/ACEI vs. treated with ARB/ACEI: 1.1±0.7 vs. 1.2±0.5 ng/ml, P=0.642) (data not shown).

Statistical differences of the mean levels of Sestrin2 and other biochemical variables according to metabolic syndrome status

The differences of mean Sestrin2 levels and other variables according to the presence or absence of MetS are presented in Table 3. Patients with MetS showed higher levels of serum Sestrin2, leptin and TNF-α, compared with patients without MetS (P=0.001, P<0.001, and P=0.042, respectively). Patients with MetS showed lower levels of adiponectin compared with patients without MetS (2533±2347 vs. 4327±3842 ng/ml, P=0.005). The

Figure 1



Serum Sestrin2 levels and diabetic nephropathy (DN). Serum Sestrin2 levels were compared between groups stratified by the presence or the absence of diabetic nephropathy. *P* value as given by independent *t* test.

Table 3 Comparisons of mean levels of Sestrin2 and other biochemical parameters according to the presence of metabolic syndrome

Index	MetS (–)	MetS (+)	*P* value
Sestrin2 (ng/ml)	1.46±0.692	1.75±0.4	0.001
TNF-α (pg/ml)	1.98±1.51	3.5±2.88	0.042
Leptin (ng/ml)	5.21±4.9	9.89±8.86	0.001
Adiponectin (ng/ml)	4327±3842	2533± 2347	0.005
FCP (ng/ml)	1.89±1.2	2.95±2.3	0.028
HOMA-IR	2.77±0.98	4.39±1.88	0.035

Data are shown as mean±SD. FCP, fasting C-peptide; HOMA-IR, homeostasis model assessment-insulin resistance; MetS, metabolic syndrome; TNF-α, tumor necrosis factor-α.

mean values of HOMA-IR and fasting plasma c-peptide were significantly higher in patients with MetS (2.77 ±0.98 vs. 4.39±1.88 ng/ml and 1.89±1.2 vs. 2.95±2.3 ng/ml, *P*=0.035 and 0.028, respectively).

Comparison of clinical and biochemical variables according to serum Sestrin2 tertiles

The participants were defined into tertiles according to serum Sestrin2 levels. The characteristics of clinical and biochemical variables according to Sestrin2 tertiles are presented in Table 4. HOMA-IR showed significant increases with increased Sestrin2 tertile values (1.49 ±1.66 vs. 1.99±1.18 vs. 3.1±3.02, *P*=0.001) (Fig. 2). Also, the prevalence of DN was significantly higher with increased Sestrin2 tertile values (*P*=0.01) (Fig. 3).

Discussion

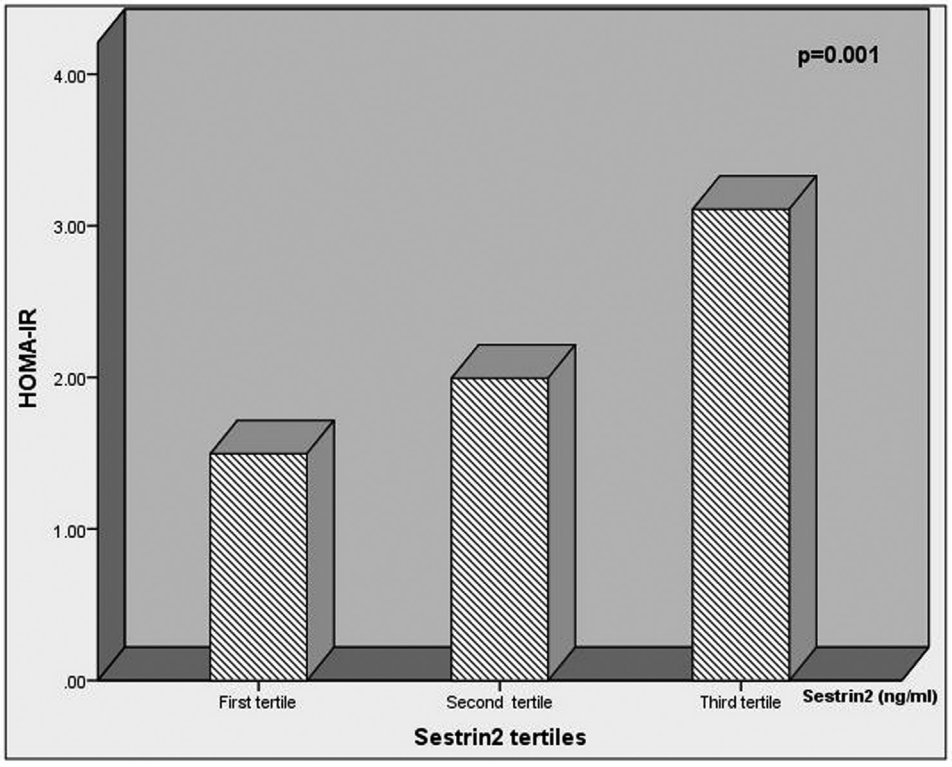
To our knowledge, this is the first study to evaluate the association of serum Sestrin2 levels with IR, MetS, and DN in patients with T2DM. Our study showed that serum Sestrin2 levels were significantly correlated with MetS and IR (measured by HOMA-IR). These results are consistent with a recent study that showed a significant association between Sestrin2 with MetS and IR [13]. In contrary to our study, Sestrin2 levels were neither correlated with IR nor significantly different in participants with MetS compared with those without MetS or those who were metabolically unhealthy compared with metabolically healthy ones [14]. There are conflicting results about the association of serum Sestrin2 with MetS that have been reported. These may be due to the strict control of the components of MetS via anti-lipidemic, antihypertensive, antidiabetic medications in addition to lifestyle modification by diabetic patients participated in our study than other study populations as such factors may act as confounding variables. Furthermore, MetS definition varies between studies. The MetS prevalence in our study was 65.8%. We found that Sestrin2 was

Table 4 Comparisons of clinical and biochemical variables according to the tertile of Sestrin2 levels

Index	First tertile	Second tertile	Third tertile	*P* value
Age (years)	54.0±8.3	51.4±9.8	52.7.3	0.612
Duration of DM (year)	7.1±5.8	6.8±5.9	7.4±6.2	0.522
Men/women	30/16	34/22	32/21	0.872
BMI (kg/m^2)	24.8±4.1	25.1±3.9	25.3±4.2	0.516
Systolic BP (mmHg)	123.2±16.1	131.2±15.2	129.5±15.7	0.031
Diastolic BP (mmHg)	75.6±9.1	76.2±8.9	75.9±8.3	0.224
FPG (mg/dl)	152.4±54.1	155.5±57.8	159.9±52.4	0.619
HbA1C (%)	7.6±1.3	7.9±1.6	7.8±1.5	0.925
eGFR (ml/min/1.73 m^2)	83.8±29.5	74.8±26.1	69.1±26.6	0.024
LDL-C (mg/dl)	90.1±27.6	92.4±27.5	94.3±29.7	0.319
Hypertension n(%)	15 (30)	17 (35.4)	19 (33.4)	0.849
FCP (ng/ml)	2.1±0.7	2.6±2.1	3.4±2.6	0.041
HDL-C (mg/dl)	47.8±11.9	46.3±12.3	48.2±14.2	0.721
Triglycerides (mg/dl)	162.5±142.3	168.3±149.8	172.1±94.2	0743
Total cholesterol (mg/dl)	171.8±32.1	177.4±37.8	171.3±34.2	0.304
hsCRP (mg/dl)	0.15±0.18	0.17±0.15	0.16±0.12	0.682
Prevalence of MetS n(%)	27(54)	33 (68.75)	45 (78.9)	0.022
Creatinine (mg/dl)	1.2±0.3	1.1±0.1	1.3±0.1	0.884
Leptin (ng/ml)	6.42±5.93	7.86±8.41	8.92±7.72	0.037
Adiponectin (ng/ml)	4272±3820	3681±3423	2679±2956	0.038
TNF-α (pg/ml)	1.65±0.96	2.9±2.98	3.6±7.61	0.042
HOMA-IR	1.49±1.66	1.99±1.18	3.1±3.02	0.001
DN	16 (32)	23 (47.9)	35 (61.4)	0.009

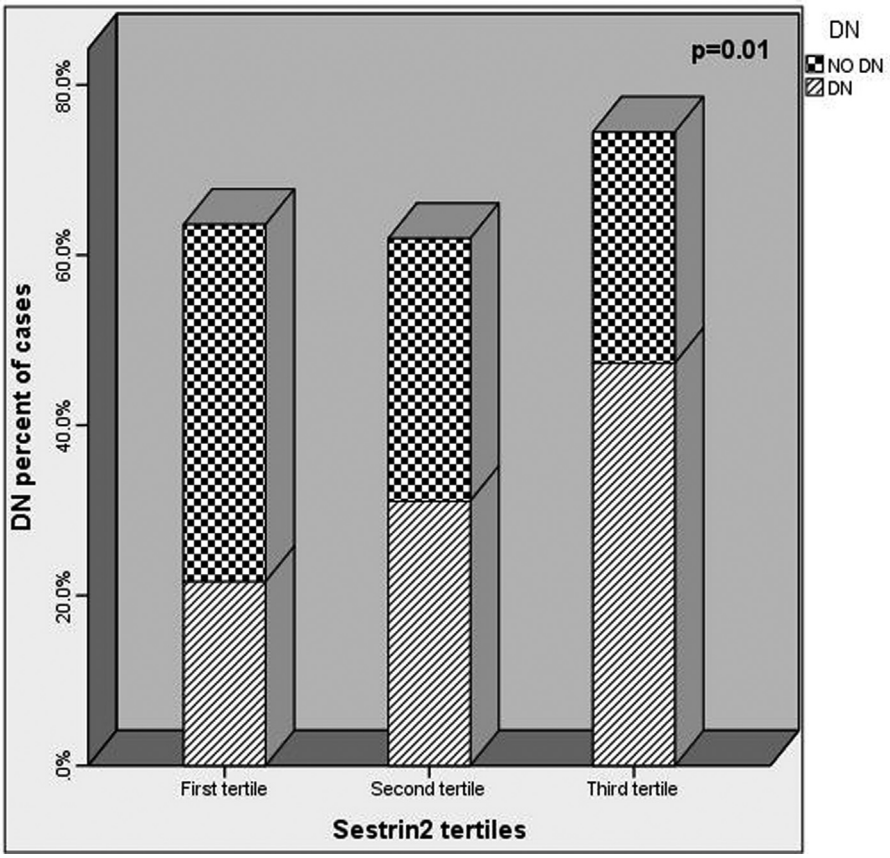
Data are shown as *n* (%) or as mean±SD. BP, blood pressure; DM, diabetes mellitus; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; FCP, fasting C-peptide; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TNF-α, tumor necrosis factor-α.

Figure 2



Mean homeostasis model assessment-insulin resistance (HOMA-IR) levels according to the tertile of Sestrin2 levels. The patients were classified into three groups by the tertiles of serum Sestrin2. HOMA-IR was compared between groups. *P* value as given by one-way ANOVA (ANOVA, analysis of variance).

Figure 3



Prevalence of diabetic nephropathy (DN) according to the tertile of Sestrin2 levels. Patients were classified into three groups by the tertiles of serum Sestrin2 levels. DN was compared between groups. *P* value as given by one-way ANOVA (ANOVA, analysis of variance).

negatively correlated with adiponectin levels. In a study by Matsushita *et al.* [15], low adiponectin level was independently associated with MetS, more than any other inflammatory markers. Hypoadiponectinemia levels are also commonly noticed in a variety of conditions that are often associated with IR, such as hypertension [16,17] and cardiovascular disease [18,19]. Many studies show that plasma adiponectin level can be regarded as a strong predictor of MetS in both sexes [20–22]. There is a contradictory relationship between adiponectin and HOMA-IR. Some researchers reported that low adiponectin levels linked to high IR in the people of South Asia [23], while others found no relationship between adiponectin and HOMA-IR [24,25]. An inverse association has been shown between adiponectin and HOMA-IR scores in Canadian native and Alaskan populations [26]. In our study Sestrin2 showed a significant positive association with serum leptin levels. Adiponectin/leptin ratio is strongly correlated with IR even stronger than leptin or adiponectin alone or HOMA-IR [27]. Furthermore, our study showed that serum Sestrin2 levels were positively correlated with TNF-α. This is the first study to demonstrate the association between Sestrin2 and TNF-α in type 2 diabetic patients. This relationship indicates that TNF-α-mediated inflammatory reaction may be associated with Sestrin2 in patients with T2DM. A study demonstrated that, in insulin sensitizing therapy, metformin activates Sestrin2 [28]. To avoid medications that may affect Sestrin2 levels, we defined the patients into a group receiving metformin (n=87) and a group not receiving metformin (n=68). No significant difference was found in serum Sestrin2 levels between both groups (group receiving metformin vs. group not receiving metformin, 1.28 vs. 1.36 ng/ml, P=0.737) (data not shown). Wang *et al.* [29] demonstrated that the Sestrin2 protein level was remarkably downregulated by angiotensin II. Serum Sestrin2 levels showed no significant differences between those treated with and without ARB/ACEI in patients with DN. In our study serum Sestrin2 levels were significantly and positively correlated with triglyceride, total cholesterol and systolic BP. This may be due to the significant association between serum Sestrin2 with adiponectin and leptin levels and their effects on lipid parameters and BP. Low adiponectin concentrations have been related to higher triglyceride and low-density lipoprotein

cholesterol levels, which may be due to the direct adiponectin effect on lipoprotein lipase activity [30,31]. In a study by Adamczak *et al.* [17], plasma adiponectin concentration was negatively correlated with systolic BP. Hypertriglyceridemia has been reported as a lipid disorder linked with high leptin concentrations [32–35]. Leptin stimulates the sympathetic nervous system activity and sodium and water reabsorption, thus increasing cardiac output, peripheral vascular resistance and BP [36]. Our observation of associations between serum Sestrin2, triglyceride, BP, and cholesterol may explain the possible pathogenetic role of Sestrin2 in the associations with the IR. There are limited data available regarding the association between serum Sestrin2 level and DN. Our study investigated the association between Sestrin2 and DN. We showed that eGFR and albuminuria were significantly correlated with serum Sestrin2 levels. Furthermore, Sestrin2 levels were associated with albumin excretion rate. In accordance with our study, Cho *et al.* [37] demonstrated that elevated Sestrin2 levels cause proteinuria in humans through the inhibition of mTOR signaling. In contrast to our study, Gödel *et al.* [38] found that mTOR inhibition can delay or reverse DN. These contradictory findings may result from the strict regulation of mTOR activity within renal epithelial cells where even little changes in mTOR activity may have significant effects [39], as the reduction of mTOR activity may lead to various cellular responses in health or disease [40]. The limitations of our study include: our study is cross-sectional, so the causative relationship between Sestrin2, IR, and DN cannot be determined. Prospective studies are recommended to address such a relationship. Also, our study includes small numbers of patients so, studies with a large number of cases are needed to confirm our results. However, the present study is significant because it is the first study that examines the associations between Sestrin2 with DN, IR, and MetS in patients with T2DM.

Conclusion

Serum Sestrin2 levels are associated with DN, IR (measured by HOMA-IR), and MetS in patients with T2DM indicating its importance as a novel prognostic marker and potential therapeutic target in DN and associated metabolic disorders. Prospective studies including greater numbers of patients are recommended to confirm the relationship between serum Sestrin2 levels and the severity or development of DN in T2DM patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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