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Research Article

Serum podocalyxin levels in patients with obesity and carbohydrates disorders

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Abstract

Background: Podocalyxin is expressed not only in glomerular podocytes but also on the endothelial cell surface outside the kidney. The aim of this cross-sectional study is to evaluate the role of serum podocalyxin as an early marker for vascular injury in patients with obesity and carbohydrate disturbances.

Subjects and methods: The study group consisted of 163 patients with a mean age of 52.5 ± 11.3 years.

Results: Levels of podocalyxin were significantly higher in healthy controls compared to patients with obesity, prediabetes, and newly diagnosed diabetes. Correlation analysis revealed that podocalyxin correlates negatively with BMI, waist circumference, waist-to-hip ratio, waist to stature ratio, fasting insulin, and one hour after the oral glucose tolerance test. ROC analyses determined that circulating podocalyxin levels are valuable for differentiating subjects with prediabetes and obesity.

Conclusion: This study is the first to assess the role of podocalyxin in the entire spectrum of metabolic disorders.

Keywords

diabetes, prediabetes, obesity, podocalyxin, metabolic disorders

Introduction

The "Diabesity" epidemic (obesity and type 2 diabetes) is likely to be the biggest epidemic in our history. The International Diabetes Federation (IDF) estimated that 537 million adults aged 20–79 years worldwide would have diabetes in 2021. This estimate is projected to rise to 643 million by 2030 and to 783 million by 2045 (IDF Atlas 2021). Although genetic factors might partially define an individual's response to environmental changes, the main factors of the global epidemic of diabetes are the rise in obesity, a sedentary lifestyle, unhealthy eating habits, and population aging (Fuchsberger et al. 2016; Chatterjee et al. 2017). Endothelial function can be negatively impacted by obesity through direct as well as indirect mechanisms, the latter resulting from obesity-related complications (diabetes, hypertension, dyslipidaemia). In many studies, a link between obesity and endothelial dysfunction was demonstrated, in which inflammation plays a central role (Tesauro and Cardillo 2011; Campia et al. 2012, 2014).

Podocalyxin (PDX), a member of the CD34 (cluster of differentiation 34) family, is a transmembrane

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sialoglycoprotein found in podocytes and is a major component of the podocyte glycocalyx. Podocytes, as visceral epithelial cells, podocytes contribute to the formation of the glomerular filtration barrier. Destruction of podocytes can result in the excretion of PDX in the urine as an early marker for kidney damage and diabetic nephropathy (Hara et al. 2012; Shoji et al. 2016). PDX also has a wide expression on the endothelial cell surface all over the body, and a recent study reported that serum PDX levels were correlated with the intima media thickness of the common carotid artery (Chen et al. 2017; Shoji et al. 2018). However, there is limited understanding of the role of podocalyxin in the early stages of metabolic disorders, such as obesity and prediabetes.

The objective of the this study was to evaluate serum podocalyxin levels in obese patients with or without carbohydrate disturbances.

Materials and methods

A total of 163 Caucasian subjects with a mean age of 52.5 ± 11.3 years were enlisted in the cross-sectional investigation, comprising 40 individuals with obesity, 42 with prediabetes, 39 with newly diagnosed type 2 diabetes, and a control group of 42 healthy volunteers.

Inclusion criteria:

- Age between 45 and 74 years.
- Obesity (BMI ≥ 30 kg/m^2).
- Impaired fasting glucose (fasting plasma glucose between 6.1 and 6.9 mmol/l) and/or impaired glucose tolerance (glucose on 120 min of OGTT between 7.8 and 11.0 mmol/l).
- Newly diagnosed type 2 diabetes (within 1 month, without previous antidiabetic therapy).

The diagnosis of diabetes mellitus was defined according to criteria of the World Health Organisation as follows: (1) fasting plasma glucose values of ≥ 7.0 mmol/L (126 mg/dl); (2) 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl); (3) HbA1c ≥ 6.5%; or (4) a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) with signs or symptoms of diabetes.

Exclusion criteria:

- Malignant disease.
- Use of oral antidiabetic drugs in the last 3 months prior to inclusion.
- Liver dysfunction (any of the hepatic enzymes > 3 times the upper limit of normal).
- Chronic kidney disease (eGFR estimated by CKD-EPI calculation < 60 ml/min/1.73 m^2).
- Heart failure (NYHA class III or IV).

Forty-two participants, with a normal BMI, no chronic diseases and no drug use were included as a control group.

The study was approved by the Science Studies Ethics Committee of the Medical University Sofia (KENIMUS) Protocol №22/05.12.2018. All patients signed an informed consent form to participate in the project.

The following methods were used in the study:

1. Anthropometric measurements included weight, height, hip circumference, waist circumference (WC), body mass index (BMI), and arterial blood pressure. BMI was calculated as weight in kg divided by the square of height in meters (BMI = kg/m^2). Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Hip circumference was measured at the level of the greater trochanter, and waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR) were calculated using the following equations: WC/hip circumference and WC/height. The estimation of VAI (visceral adiposity index) was performed using the following formula:

VAI = (WC / (36.58 + (1.89 × BMI) x (TG / 0.81) × (1.52 / HDL) for women; VAI = (WC / (36.68 + (1.88 × BMI) × (TG / 1.03) x (1.31 / HDL) for men.

   Body impedance (BIA) by a TANITA™ TBF-215 GS Body Composition Analyzer in the fasting state was used to evaluate the percentage of body fat (body fat%).
2. Investigation of carbohydrate metabolism: An oral glucose tolerance test (OGTT) with measurements of glucose and immunoreactive insulin (IRI) (ECLIA, Roche Diagnostics™) at 0 min, 60 min, and 120 min. The HOMA index (fasting glucose X fasting immunoreactive insulin) / 22.5) was calculated. Insulin resistance was assumed if the HOMA index was > 2.5.
3. The presence of metabolic syndrome (MS) was determined based on the IDF criteria (Alberti et al. 2009). Patients were considered to have MS if they met at least 3 of the following criteria: 1) abdominal obesity, defined as waist circumference ≥ 94 cm for men and ≥ 80 cm for women; 2) elevated blood pressure, defined as systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic blood pressure (DBP) ≥ 85 mm Hg, or current antihypertensive drug treatment; 3) elevated fasting blood glucose level ≥ 5.6 mmol/l, the current use of blood glucose lowering agents or history/diagnosis of type 2 diabetes; 4) decreased HDL cholesterol levels (<1.03 mmol/l in men or < 1.30 mmol/l in women) or drug treatments aimed at increasing HDL cholesterol; and 5) hypertriglyceridaemia (triglyceride level ≥ 1.70 mmol/l) or drug treatment for elevated triglycerides.
4. Measurement of intima-media thickness (IMT) by Panasonic CardioHealth station (Panasonic, Japan), ankle-brachial index (ABI) (Elite Natus, USA); assessment of the autonomic nervous system via the evaluation of sudomotor function with FDA-ap-

proved Sudoscan (Itamar Medical Israel); and assessment of the peripheral nervous system true neuropathy disability score.

5. Measurement of serum podocalyxin was performed by enzyme-linked immunosorbent assay (ELISA) (My BioSource, USA). Sensitivity: The minimum detectable dose of human endocan is typically less than 0.053 ng/ml. Serum samples were obtained after an overnight fast and were then immediately centrifuged for 15 minutes at 4000 rpm; subsequently, the serum was stored at -80 °C until the tests were performed.

Statistical analysis

The data were processed using the statistical package SPSS 25.0 (IBMTM). The level of significance for rejecting the null hypothesis was $p < 0.05$. The following statistical methods were applied:

1. Descriptive analysis: the frequency distribution of the considered signs, broken down by research groups, is presented in tabular form.
2. Variation analysis: calculation of estimates of central tendency and dispersion.
3. Kolmogorov-Smirnov test: to examine the distribution's normality. In cases where data displayed a normal distribution, parametric tests were applied, with the outcomes presented as mean differences along with their respective standard deviations (SD). Conversely, when data distribution exhibited skewness, a nonparametric test was employed to compare variables, and the hypotheses are expressed as differences between medians, represented by the interquartile range [IQR].
4. One-way analysis of variance ANOVA: to test hypotheses about a difference between independent samples.
5. Student's t-test: for testing hypotheses about the difference between two independent samples.
6. Non-parametric Kruskal-Wallis test: to test hypotheses of differences between several independent samples.
7. Non-parametric Mann-Whitney test: to test hypotheses of differences between two independent samples.
8. Pearson's correlation analysis: for normally distributed data.
9. Spearman's correlation analysis: for non-normal distribution.
10. Multivariate logistic regression: for determination of the adjusted odds ratios (ORs) and 95% confidence intervals for the predictive value of podocalyxin for various metabolic disorders.
11. ROC curve: to determine threshold values of quantitative signs for the purpose of the classification of certain conditions.

Results

The study included 163 patients with an average age of 52.5 ± 11.3 years, divided into four groups: group 1 (control group), consisting of healthy volunteers with a normal BMI and no disturbances (n = 42); group 2, obese without glycaemic disturbances (n = 40); group 3, subjects with prediabetes (n = 42); and group 4, patients with newly diagnosed type 2 diabetes (n = 39) Table 1 demonstrates the characteristics of the four different groups. In the prediabetes group, 17 patients (40.48%) had impaired fasting glucose (IFG), 22 (52.38%) had impaired glucose tolerance (IGT), and 3 (7.14%) had IFG+IGT.

The four groups did not differ in age; however, those with obesity, prediabetes, and diabetes had higher BMI, WSR, WHR, VAI, and WC compared to the control group. Patients with diabetes also had higher levels of fasting glucose, HOMA, triglycerides, and systolic blood pressure, as well as lower levels of HDL compared to subjects with prediabetes and obesity. Additionally, a higher percentage of patients with diabetes had dyslipidaemia compared to those with obesity (Table 2).

We found higher levels of serum podocalyxin in healthy controls compared to patients with obesity, prediabetes, and newly diagnosed diabetes (1.82 ± 0.37 vs. 1.50 ± 0.45; vs. 1.66 ± 0.98; vs. 1.60 ± 0.50 ng/ml, $p < 0.05$) (Fig. 1). There was a negative correlation between the level of podocalyxin and BMI ($r=-0.279$; $p < 0.001$), waist circumference ($r=-0.207$; $p = 0.008$), waist to hip ratio (WHR) ($r=-0.211$; $p = 0.023$), waist to stature ratio (WSR) ($r = -0.232$; $p = 0.003$), fasting insulin ($r = -0.209$; $p = 0.033$), and in the first hour after oral glucose tolerance test (OGTT) ($r = -0.202$; $p = 0.042$) (Table 3). ROC-curve analysis was performed to determine whether podocalyxin can be used to distinguish early carbohydrate disturbances, specifically prediabetes and obesity. The AUC was 0.739 ($p < 0.001$) and the cutoff value of ≤ 1.75 ng/ml had a sensitivity of 81% and specificity of 62% to distinguish prediabetes, whereas the AUC for obesity was 0.784 ($p < 0.001$) with a cutoff value of ≤ 1.61 ng/ml, sensitivity of 73%, and specificity of 79%.

Table 1. Anthropometric characteristics of the study groups.

	Controls (a)	Obesity (b)	Prediabetes (c)	Diabetes (d)	a/b	a/c	a/d	b/c	b/d	c/d
N	42	40	42	39						
Age, yrs	45 (23)	53 (18)	55 (21)	57 (17)	ns	Ns	ns	ns	ns	ns
BMI (kg/m²)	23.1 (2.2)	34 (3.4)	35 (8.3)	34 (7.5)	<0.001	<0.001	<0.001	ns	ns	ns
Waist, cm	79 (14)	104 (15)	106 (19)	105.5 (15)	<0.001	<0.001	<0.001	ns	ns	ns
WHR	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001	<0.001	ns	ns	ns	ns
WSR*	0.5 [0.0]	0.6 [0.1]	0.6 [0.1]	0.7 [0.1]	<0.001	<0.001	<0.001	ns	ns	ns

Values are represented as the median (IOR) if distribution was not normal or the mean [SD] (marked with *) when distribution was normal.

Table 2. Cardiovascular risk factors.

	Obesity (b)	Prediabetes (c)	Diabetes (d)	b/c	b/d	c/d
N	40	42	39			
SBP (mmHg)	130 (20)	135 (23)	140 (30)	ns	ns	ns
DBP (mmHg)	80 (10)	80 (10)	80 (20)	ns	ns	ns
Tchol* (mmol/l)	5.1 [0.9]	5.3 [1.0]	5.7 [1.1]	ns	p = 0.006	ns
LDL * (mmol/l)	3.1 [0.7]	3.2 [1.0]	3.4 [1.0]	ns	ns	ns
HDL (mmol/l)	1.3 (0.3)	1.2 (0.5)	1.1 (0.3)	ns	ns	ns
TG (mmol/l)	1.4 (0.8)	1.6 (1.0)	1.9 (1.4)	p = 0.035	p = 0.001	ns
Hypertension % (number)	75% (30)	85.7% (36)	92.3 (36)	ns	ns	ns
Smoking % (number)	27.5% (11)	16.7% (7)	38.5% (15)	ns	ns	ns
Dyslipidaemia %(number)	57.5% (23)	66.7% (28)	82.1% (32)	ns	p = 0.017	ns

Tchol: total cholesterol; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure. Values are represented as the median (IOR) if distribution was not normal or the mean [SD] (marked with *) when distribution was normal.

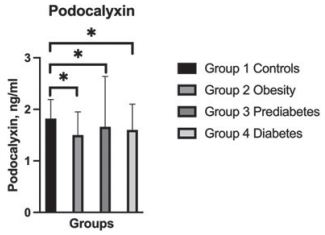

Figure 1. Serum podocalyxin between the groups.

Table 3. Spearman correlations of circulating serum podocalyxin with different parameters of the study population.

Variable	R	p
Age	-0.124	0.115
BMI (kg/m²)	-0.279	**<0.001**
WC (cm)	-0.207	**0.008**
WHR	-0.211	**0.023**
WSR	-0.232	**0.003**
VAI	-0.016	0.586
SBP (mmHg)	-0.117	0.203
DBP (mm Hg)	-0.080	0.385
Tchol (mmol/l)	-0.155	0.094
LDL (mmol/l)	-0.167	0.071
HDL (mmol/l)	-0.062	0.504
TG (mmol/l)	-0.032	0.731
Creatinine (mkmol/l)	0.098	0.283
Uric acid (mkmol/l)	-0.007	0.938
ASAT (U/l)	-0.019	0.838
ALAT (U/l)	-0.112	0.225
GGT (U/l)	-0.072	0.442
Fasting Glucose (mmol/l)	0.129	0.158
Glucose 60 min (mmol/l)	-0.041	0.689
Glucose 120 min (mmol/l)	0.078	0.444
Fasting IRI (mU/l)	-0.209	**0.033**
OGTT 60' IRI (mU/l)	-0.202	**0.042**
OGTT 120' IRI (mU/l)	-0.082	0.425
HOMA	-0.062	0.542
Biothesiometer	0.284	**0.002**
NDS	0.211	**0.021**

BMI: body mass index; WHR: waist to hip ratio; WSR: waist to stature ratio; VAI: visceral adiposity tissue; SBP: systolic blood pressure; DBP: diastolic blood pressure; Tchol: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; Gluc: glucose; IRI: immunoreactive insulin; NDS: neuropathy disability score; Bioth: biothesiometer.

We also investigated the association between serum podocalyxin and some markers for microvascular complications. We found a positive correlation between podocalyxin and neuropathy disability score (NDS) (p = 0.021) and biothesiometer (p = 0.002).

Discussion

This report is the first to compare serum podocalyxin levels in all stages of glucose tolerance among subjects with a matched sex distribution and age. Our aim was to evaluate the role of the marker as a predictor of earliest metabolic disorders by selected individuals without prior therapy, which itself could reflect on levels of serum podocalyxine. As podocalyxin levels decreased with worsening glycaemia, it is feasible that podocalyxin might be involved in the pathogenesis of type 2 diabetes.

It is well known that type 2 diabetes is associated with micro- and macrovascular complications. There is evidence that the increased risk of developing micro- and macrovascular damage in individuals with prediabetes may present long before they are diagnosed with diabetes. In many instances, endothelial dysfunction starts to develop during the prediabetic phase and has already become established by the time diabetes becomes apparent (Souza et al. 2012; Huang et al. 2017; Zand et al. 2018). There are several pathogenic mechanisms for the development of micro- and macrovascular complications in prediabetes. These include the pro-inflammatory state, insulin resistance, endothelial dysfunction, and prothrombogenic conditions, which are observed even in the earliest stages of metabolic disorder—obesity without glycaemic disorders (Brannick and Dagogo-Jack 2018; Rett and Gottwald-Hostalek 2019; Ahmed et al. 2021; Rosolová 2022).

Podocalyxin was initially identified as an apical membrane protein belonging to the CD34 family (Kerjaschki et al. 1984). It serves as an early marker for diabetic nephropathy and is considered a biomarker for glomerular damage (Suwanpen et al. 2015). It is now understood that podocalyxin is not only expressed in kidney glomeruli but also on the surfaces of vascular endothelial cells,

mesothelial cells, haematopoietic progenitors, and neurons (Maltby et al. 2010; Vitureira et al. 2010; Chen et al. 2017). In addition to being an early marker of glomerular damage and diabetic nephropathy, urinary and serum levels of podocalyxin are relevant to endothelial function and vascular inflammation (Mansilla et al. 2018).

This study focused on serum podocalyxin because it is expressed on endothelial cells. The *in vivo* functions of podocalyxin in vascular cells have been studied, and it has been reported that endothelial cell-specific deletion of the podocalyxin gene in an animal model increased lung volume, basal inflammation, and vascular permeability. The lack of podocalyxin in endothelial cells shows a weak potential to spread on a laminated dish (Debruin et al. 2014). Another study reported that there was an increase in nonspecific inflammatory infiltrates within the vessels and CRP level in murine endothelial cells after conditional knockout of the Podxl gene. Furthermore, the study showed that endothelial cells lacking Podxl show persistent F-actin stress fibres and delayed recovery of vascular endothelial cadherin cell contacts after thrombin stimulation (Horrillo et al. 2016). Together, these reports indicated that podocalyxin possesses a crucial role not only for endothelial cell adhesion and barrier stabilisation but also for reducing inflammation.

Data on the role of podocalyxin in the pathogenesis of vascular damage in individuals with disorders of carbohydrate metabolism are scarce. Higher levels of serum podocalyxin have been reported in patients with diabetes mellitus and peripheral arterial disease compared with diabetics without evidence of macrovascular damage (El-Ashmawy et al. 2019). Xie et al. (2022) demonstrated that the levels of podocalyxin in the urine are increased in the early stages of diabetic nephropathy, even in the presence of normal albuminuria.

In our study, we found significantly higher levels of serum podocalyxin in the control group of healthy individuals compared to the other three pathological groups: patients with obesity, prediabetes, and newly diagnosed diabetes. In addition, statistically significantly lower levels of serum podocalyxin were observed in subjects with obesity compared to those with a normal body mass index. Moreover, those with levels ≤ 1.78 have a correspondingly 6.9 times higher risk of obesity compared to individuals with higher levels.

We speculate that these differences with our results might be due to the fact that our patients had earlier disturbances in carbohydrate metabolism, namely prediabetes and newly diagnosed diabetes mellitus with correspondingly lower glycaemic levels, without antidiabetic treatment, which can influence the levels of serum podocalyxin. Furthermore, there was no definitive data on available macrovascular complications from the current study population.

Additionally, we found a negative correlation between serum podocalyxin levels and body mass index, waist circumference, waist-to-hip and waist-to-height ratios, fasting insulin, and insulin at 60 minutes during the OGTT. These results, in addition to our observed lower levels of podocalyxin in subjects with obesity and/or carbohydrate disorders, lead us to suggest that there are likely additional mechanisms by which podocalyxin is involved in metabolic disorders, and further studies are needed to support this hypothesis.

Regarding our instrumental studies, we found for the first time a positive correlation between serum podocalyxin levels and the peripheral neuropathy index (NDS), as well as vibration sensitivity assessed with a biothesiometer. Until now, there has been a lack of convincing data on the role of podocalyxin in the pathogenesis of neurological damage.

The limitations of our study include the relatively small sample size and a younger control group, as well as the cross-sectional design, which renders the determination of a possible cause-effect relationship impossible. In the future, our scientific goals are to increase the number of the studied population group, which will contribute to greater statistical significance. Furthermore, we plan to evaluate the changes in the serum levels of podocalyxin after a three-month diet aimed at reducing body weight by at least 5%. The results will elucidate the relationship between the new markers for endothelial dysfunction and the chonic complex disease of obesity.

Conclusion

Serum podocalyxin is decreased in patients with obesity, prediabetes, and newly diagnosed diabetes in comparison to healthy individuals. Podocalyxin is associated with an increased risk of obesity and early carbohydrate disturbance.

Author contributions

All authors contributed to the study design, data analysis and interpretation, and critical review of the manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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