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Assessment of brain-derived neurotrophic factor and irisin concentration in children with chronic kidney disease: a pilot study

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Abstract

Patients suffering from chronic kidney disease (CKD) are particularly placed at risk of multiorgan complications. One of them is malnutrition, which adds up to a higher mortality factor among them. This study was designed to determine the usefulness of brain-derived neurotrophic factor (BDNF) and irisin assays in the assessment of CKD development. The study group included 28 children with CKD at stages 2-5 treated conservatively. The outcome of our study revealed decreased serum BDNF and irisin levels in CKD patients, whereas urine concentrations were increased for BDNF and decreased for irisin, comparing to healthy controls. There was a positive correlation between anthropometric measures and urine BDNF concentration, as well as anthropometric measures and both serum and urine irisin levels in the study group, however no dependence of the tested markers on the stage of CKD was observed. In recent years, a role of myokines was described as vital for maintaining metabolic homeostasis therefore we suspect a potential role of these multifaceted markers in detecting malnutrition in CKD children.

Keywords Brain-derived neurotrophic factor, Irisin, Chronic kidney disease, Malnutrition

Introduction

Chronic kidney disease (CKD) remains a worldwide public health problem. Recent data suggests that 9,1% to 13,4% of the global population suffers from this condition [1, 2]. The proportion of young patients is much lower, however the data on the prevalence of CKD among children are scarce. The 2007 research presented CKD incidence in childhood reaching 15 to 74.7 cases per million of the age-related population (pmarp) [3]. Such variation in morbidity might be caused by different etiology, determined by the age group. While in adulthood diabetes and hypertension are the main causes of CKD, congenital abnormalities of the kidney and urinary tract (CAKUT) most frequently lead to development of this disease in children [4, 5].

Regardless of the origin of CKD and patient's age, progressive loss of the kidney function is observed, eventually leading to end stage renal disease (ESRD). It has been established, that in stage 3b CKD, which stands for eGFR lower than 45 ml/min/1,73m2, a substantial impairment of system's compensatory mechanisms occurs, therefore patients in stages 3b-5 are at greater risk of CKD complications [6], such as anemia, metabolic acidosis,

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electrolyte imbalance, mineral and bone disorder, as well as cardiovascular diseases [7, 8].

Moreover, both young and adult patients are considerably more likely to be malnourished. Consequently, malnutrition, alongside with somatotropic axis disorders, are believed to be the main causes of short stature in children with CKD [9]. It is estimated, that among 30-60% children with ESRD, short stature is observed in the adulthood [8]. Such problem was encouraging to search for new diagnostic strategies for malnutrition in CKD patients. Malnutrition in CKD is a result of several events, permanently inscribed in the disease's clinical picture. Aside from loss of appetite and lower nutrient intake, decreased protein synthesis and increased catabolism is observed [9] (Fig. 1).

The American Society for Parenteral and Enteral Nutrition defines malnutrition as an imbalance between nutrient requirement and intake resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes [10]. Protein energy wasting (PEW) is a significant complication in CKD patients, including children, as it may increase the risk of morbidity, mortality and overall disease burden [8, 9, 11]. In 2020, Kidney Disease Outcomes and Quality Initiative Committee (KDOQI) published the Clinical Practice Guideline for Nutrition in CKD for adults, however most recent recommendations for children were written in 2008 [12, 13]. According to KDOQI, main tools to assess nutritional status in young population are weight, height and BMI [12]. Due to the existing need for more sensitive guidelines, modified criteria of PEW in children are proposed by Abraham et al. or Iyengar et al. [11, 14].

Multifaceted role of brain derived neurotrophic factor (BDNF) and irisin

In light of the studies evaluating the usefulness of BDNF and irisin as potential markers of CKD, we would like to point out the multifactorial nature of the studied molecules. The results we obtained, as well as researches assessing their involvement in the nutrition process, prompted us to look at them in the context of markers of nutritional status rather than isolated markers of CKD.

BDNF, one of the most well-known neurotrophins, is said to be stimulating nerve growth. Synthesized as an immature form with high p75 neurotrophin receptor (p75NTR) affinity, is then converted by proteolysis into mature form of neurotrophin, that acts mainly through tropomyosin-related kinase B (TrkB) receptor [15, 16]. BDNF serves as a major neuronal survival factor, as well as supports differentiation, growth and longterm potentiation (LTP) of neurons [15, 17]. Despite its substantial role in CNS, BDNF has been described to be vital in various tissues and organs, including kidneys [16, 18, 19]. In previous studies of CKD, correlations between neither BDNF expression, glomerular filtration rate (eGFR) nor CKD stage were observed [18, 20]. Nevertheless, researches show that individuals with decreased serum

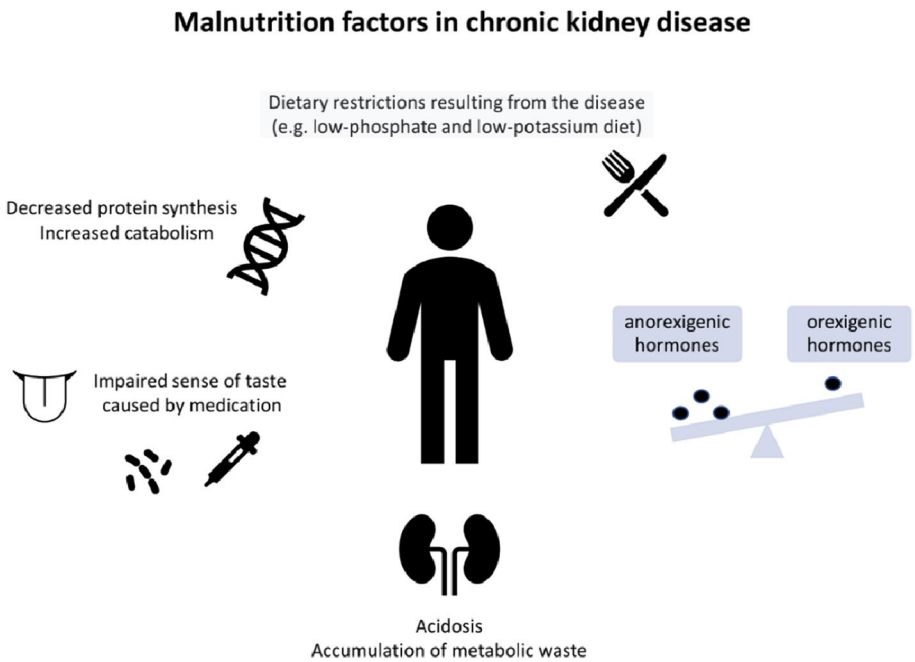

Fig. 1 Malnutrition factors in CKD

BDNF concentration were more likely to develop CKD, compared with those with a higher concentration and had high all-cause mortality rate [21, 22].

According to literature, this neurotrophin is also secreted by skeletal muscles, therefore being an autocrine and paracrine signaling myokine, it has been assessed as an obesity and anorexia promoting factor [23]. BDNF influences nutrition not only as a myokine, but also by affecting central regulation of food intake, by involvement in hypothalamus and especially the dorsal vagal complex (DVC) processes, involved in the regulation of feeding [24–26]. BDNF is reckoned as anorexigenic factor, as its low levels increase appetite [20, 27]. In turn, insufficient expression of BDNF and TrkB receptors may lead to obesity [28]. In addition, discrepancies occurring in the literature also pertain to serum BDNF levels in patients with anorexia nervosa (AN). Keeler et al. suggested an adaptive response to a chronic starvation in patients with AN, that would lead to increased appetite, whereas decreased serum BDNF concentration occurred in this group, compared with healthy controls [27, 29].

In contrast to the long research conducted on BDNF, irisin is a relatively recently discovered myokine (known since 2012), and is still a field of discussion. It was first described as a polypeptide induced by physical exercises [30]. Its molecular structure is based on a fibronectin type III domain, which begins from FNDC5 gene (fibronectin type III domain containing protein 5) product [31]. The literature shows, that Ir is involved in thermogenesis by supporting the process of turning white adipose tissue (WAT) into brown adipose tissue (BAT) [31–33]. A recent study shows a decrease in serum Ir concentrations in patients with anorexia nervosa (AN) compared to control group by 15 % and to obese patients by 30, therefore, as in the case of BDNF, the question arises whether this is an adaptive response of the organism [32, 34].

Also role of Ir in obesity, diabetes mellitus, coronary artery disease, metabolic syndrome, and chronic inflammation, conditions closely associated with CKD, is well demonstrated in the literature [35]. However, to this point, its influence on kidneys is mainly described in acute and chronic decline in renal filtration function. Renoprotective effect of Ir in renal ischaemia and sepsis was reported in studies with animal models [36, 37], while in other studies it was noted, that its concentration decreases with higher CKD stage [35, 38, 39].

Main aims of the study

Up to this point, there is limited knowledge on mechanisms, that would prevent the development of CKD, while the complications of the disease lead to patients' poor overall condition and increase fatality. In our study we aimed to assess BDNF and Ir as potential markers for CKD in pediatric population, especially considering the correlation with malnutrition.

Materials and methods

Description of analyzed groups of patients

The study group included patients with a diagnosis of chronic kidney disease (n = 28) and admitted to the Department of Pediatric Nephrology with the Subdivision of Dialysis at the Clinical Hospital No. 1 in Zabrze, Medical University of Silesia in Katowice in the period from October 2019 to November 2021. Inclusion criteria for this group were: confirmed diagnosis of CKD stage 2-5, children older than 12 months and younger than 18 years of age. The exclusion criteria included: patients undergoing dialysis, patients with exacerbation of CKD and patients after kidney transplantation. The information about the cause of CKD and the date of diagnosis, occurring complications, co-morbidities and administered medicine were obtained. The control group (n = 44) was represented by children hospitalized in the same period of time in the Department of Pediatric Nephrology with the Subdivision of Dialysis at the Clinical Hospital No. 1 in Zabrze, due to bedwetting or in the Department of Surgery of Child Developmental Defects and Traumatology of the Clinical Hospital No.1 in Zabrze, Medical University of Silesia in Katowice as patients undergoing one-day surgery. In this group no chronic diseases nor infectious diseases were diagnosed and all the children had normal kidney function. This study project got the approval of the Ethical Council of the Medical University of Silesia in Katowice (KNW/0022/KB1/31/I/19). The researchers collected a written informed consent from all children caregivers and also from children 16 years old or above. Blood and urine samples were collected from fasting paticipents where the patient was over 3 years old. In case of a younger children, no attention was paid to fasting. Biochemical tests such as serum creatinine, serum urea, serum uric acid, total serum protein concentration, albumin blood test, cholesterol level, level of triglycerides, parathyroid hormone test, blood ionogram, blood gas test, and urinalysis as well as complete blood count were obtained from each participant. The classic Schwartz formula with the age-appropriate k-coefficient (ml/min/1.73 m2) was used to evaluate eGFR. BDNF serum and urine levels were estimated by the Cloud-Clone (USA)-Human BDNF kit, catalog number SEAO11Hu, according to technological instructions sent by the manufacturer. SYNERGY/H1 reader (BioTek, Santa Clara, CA, USA), at 450 mm wavelength, using 620 nm wavelength as a reference, was used to take absorbance readings. Then, the Gen5 v 3.05 computer program (BioTek, Santa Clara, CA, USA) served as a tool to elaborate the results. The sensitivity of the method was

estimated at 11.7 pg/ml. The precision in the simultaneous series (imprecision) reached 3.8Ir serum and urine concentrations were assessed using ELISA technique with Bio-Vendor (Czech Republic)- Human IRISIN ELISA nr RAG018R kit. The analytic procedure was performed in accordance with a guidance from producers. Again, absorbance readings were obtained using SYNERGY/H1 reader (BioTek, Santa Clara, CA, USA), at 450 mm wavelength, using 620 nm wavelength as a reference, as well as the Gen5 v 3.05 computer program (BioTek, Santa Clara, CA, USA) was used to elaborate the results. Sensitivity of the method reached 1.0 ng/ml. The precision in the simultaneous series (imprecision) was estimated at 4.86Anthropometric parameters were measured for the whole group of children. Kilograms were used to assess weight (with 0.01 kg precision) and centimeters to estimate height, using a standardized stadiometer (with 0.01 cm precision). Calculation of BMI was then performed using the equation: weight/height2 (kg/m2). OLA and OLAF trials for population of polish children was used to plot weight, height and BMI for age and sex on percentile charts [40]. We also calculated SDS values for body weight, height and BMI to be able to compare those values in different age groups. No data was missing in the evaluated cohorts.

Statistical analysis

Quantitative variables were assessed using Shapiro Wilk test and then presented as median with interquartile range for all variables due to the fact, that almost all of them, except anthropometric measurements were non-normally distributed. To compare variables between two groups Mann Whitney- U test was used. Spearman's coefficient served to determine correlations between variables. ROC analysis was performed to estimate the value of analyzed variables as potential biomarkers of CKD. Cutoff point was obtained by Youden method, results of analysis were presented as sensitivity, specificity and area under curve (AUC) with 95% confidence interval. *P* values < 0,05 were considered significant. Analysis was performed using R language in Rstudio Environment.

Results

There were 72 children participating in the research. The study group included 28 individuals, 11 (39,3 %) girls and 17 (60,7 %) boys, with CKD stage 2-5, with the exclusion of dialysis patients. The control group was represented by 44 children, 18 (40,9 %) girls and 26 (59,1 %) boys, with no medical history of kidney disorders, neither congenital nor acquired. The age of the participants varied from 1.17 to 18.00 in the study group, the median age was 9.5 (6.25-15.33), and from 2.0 to 17.5 years in control group, the median age was 7.75 (6.38-11.83). Significant differences were noted neither in the gender distribution (p = 0.99, Fisher's test) Table 1 nor the age (p = 0.612) between the groups. No significant differences were found between the groups considering anthropometric measures, apart from SDS weight and SDS height Table 1. The results of laboratory tests in the study group and in separate subgroups are presented in Tables 2 and 3

A group of boys and girls with CKD was compared in terms of biochemical parameters, which may be disrupted in CKD. However, apart from uric acid levels, no statistically significant differences were found. It is known that hyperuricemia may be responsible for faster CKD progression. It is important to confirm that they exist in the studied group differences depending on gender, despite pediatric age.

Comparing the serum and urine levels of BDNF and Ir in the groups, it occurred, that significantly lower

Table 1 Characteristics of the groups- selected anthropometric and laboratory parameters (Mann Whitney Wilcoxon test)

Parameter	Control group (n=44)			Study group (n=28)			
	median	Q1	Q3	median	Q1	Q3	p
Height (cm)	127	120	155	133	113	154	0,56
Height SDS	0,09	-0,86	0,81	-1,23	-1,88	-0,341	<0,01
BW (kg)	27,1	21	45	29,8	21	44,4	0,73
BW SDS	0,065	-0,805	0,838	-0,771	-1,54	-0,06	<0,01
BMI (kg/m2)	16,6	14,8	19,9	16,9	15,8	19,2	0,38
BMI SDS	-0,055	-0,812	0,775	-0,08	-0,798	0,955	0,90
Serum BDNF (ng/ml)	1,02	0,874	1,19	0,638	0,54	0,735	<0,001
Urine BDNF (ng/ml)	0,798	0,591	0,933	1,23	1,11	1,46	<0,01
Serum irisin (ng/ml)	332	300	401	171	152	202	<0,001
Urine irisin (ng/ml)	91,2	80	96,7	54,2	49,2	63,8	<0,01

Q1: first quartile; Q3: third quartile; p: *p*-values for Mann Whitney Wilcoxon test, SDS: standard deviation score; BW: body weight; BMI: body mass index

Table 2 Characteristics of the study group- selected anthropometric and laboratory parameters

Parameter	Female			Male			
	median	Q1	Q3	median	Q1	Q3	p
Height (cm)	136	122	161	130	88	150	0,371
Height SDS	-0,417	-1,24	-0,227	-1,5	-2,8	-0,593	0,053
BW (kg)	28,5	22,9	46,4	31	14,8	43,9	0,244
BW SDS	-0,686	-0,981	0,003	-1,5	-1,75	-0,154	0,195
BW percentile	36,0	16,5	49,5	10,0	7,0	45,0	0,22
BMI (kg/m2)	16,8	16	17,9	17,7	15,7	19,5	0,925
BMI SDS	0,216	-0,629	0,979	-0,381	-0,829	0,95	0,677
Serum BDNF (ng/ml)	0,771	0,536	0,855	0,638	0,551	0,655	0,187
Urine BDNF (ng/ml)	1,21	1	1,59	1,27	1,15	1,33	0,677
Serum irisin (ng/ml)	171	163	194	164	144	208	0,61
Urine irisin (ng/ml)	53,2	51	77,1	55,2	47,8	61,3	0,144

Q1: first quartile; Q3: third quartile; p: *p*-values for Mann Whitney Wilcoxon test, SDS: standard deviation score; BW: body weight; BMI: body mass index

Table 3 Characteristics of the study group- selected laboratory parameters

Parameter	Female			Male			
	median	Q1	Q3	median	Q1	Q3	p
Albumin (g/l)	47,4	41,9	47,8	45,3	42,4	47,2	0,677
Creatinine (umol/l)	118,0	67,0	308,0	179,0	117,0	230,0	0,547
eGFR (ml/min/1,73m2)	45,0	17,2	61,8	26,0	13,8	43,5	0,258
HCO3 (mmol/l)	22,7	22,0	24,8	22,0	20,0	25,5	0.588
Hb (g/dl)	11,9	11,3	13,2	11,1	10,3	12,9	0,437
PTH (pg/ml)	56,9	38,5	242,0	101,0	45,0	222,0	0,748
Total protein (g/l)	71,3	70,2	74,4	70,3	64,8	73,3	0,311
Triglycerides (mmol/l)	1,0	0,7	1,7	1,1	0,9	2,2	0,289
Urea (mmol/l)	7,2	6,5	14,4	15,9	8,5	18,6	0,869
Uric acid (umol/l)	352	309	426	390	268	407	0,038
HDL (mmol/l)	1,48	1,27	1,79	1,39	1,11	1,63	0.663

Q1: first quartile; Q3: third quartile; p: *p*-values for Mann Whitney Wilcoxon test, eGFR: estimated glomerular filtration rate; HCO3: bicarbonate; Hb: hemoglobin; PTH: parathormone; HDL: high-density lipoprotein

serum BDNF level and significantly higher urine BDNF level were observed in the study group. Moreover, Ir serum and urine levels were significantly lower in the study group (Fig. 2).

Then, a detailed analysis of the correlation of selected parameters was performed (Fig. 3). There was a positive correlation between serum and urine BDNF levels in the control group. A significant positive correlation was also found between urine irisin and serum irisin levels in the control group. In the study group, we did not observe any correlation between the urine and serum concentrations of the tested markers.

A significantly lower urine BDNF level was also observed among patients with albuminuria, defined as 24-hour urinary albumin excretion (UAE) equal to or greater than 30 mg/day or albumin/creatinine ratio (ACR) >30 mg/g (Fig. 4). There were no other dependencies due to albuminuria.

The ROC curves show the true positive rate (sensitivity) and false positive rate (1-specificity) of the diagnosis when the marker (here: BDNF or irisin level) is thresholded. The area under the ROC curve (AUC) measures overall diagnostic accuracy, with an AUC of 100% representing perfect discrimination and an AUC of 50% representing random chance. In our study, ROC curve analysis for the tested markers showed that all the parameters were characterized by good sensitivity and specificity as potential disease markers, with AUC of 91% or higher in all cases (Figs. 5, 6, 7, and 8).

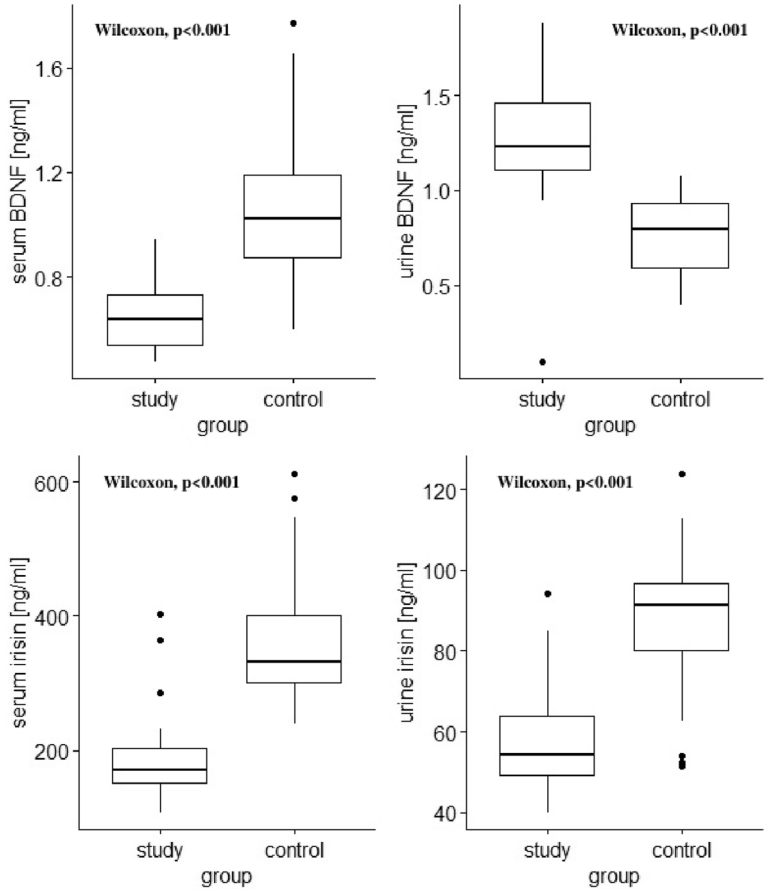

Fig. 2 Comparison of BDNF concentration in serum (**A**) and urine (**B**) between the control group and the study group (Mann Whitney Wilcoxon test). Comparison of irisin concentration in serum (**C**) and urine (**D**) between the control group and the study group (Mann Whitney Wilcoxon test)

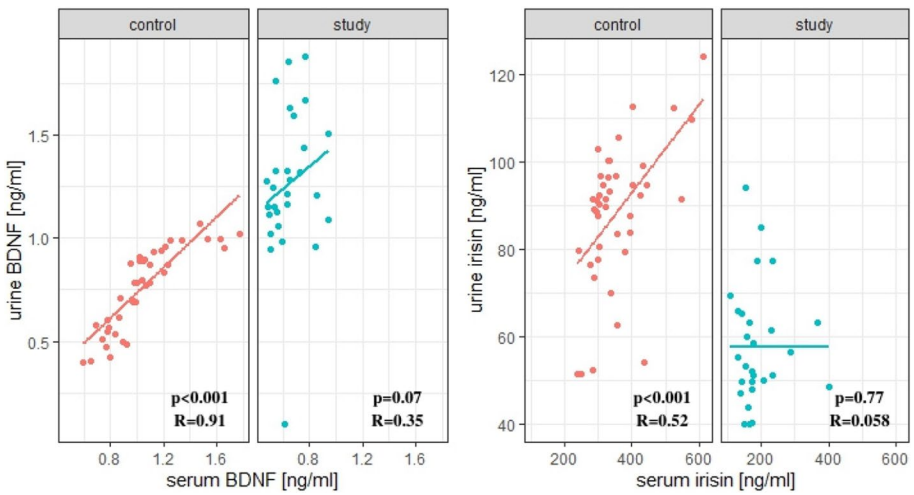

Fig. 3 Correlation between the concentration of BDNF in the serum and urine (**A**) and of irisin in the serum and urine (**B**), taking into account the division into the study group and the control group (Spearman's correlation coefficient)

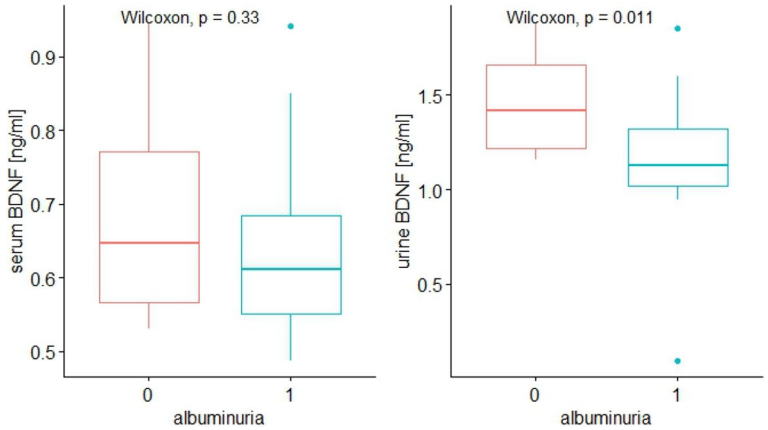

Fig. 4 The comparison of BDNF concentration in the study group in serum (**A**) and urine (**B**) between the patients without albuminuria (0) and with albuminuria (1), (Mann Whitney Wilcoxon test)

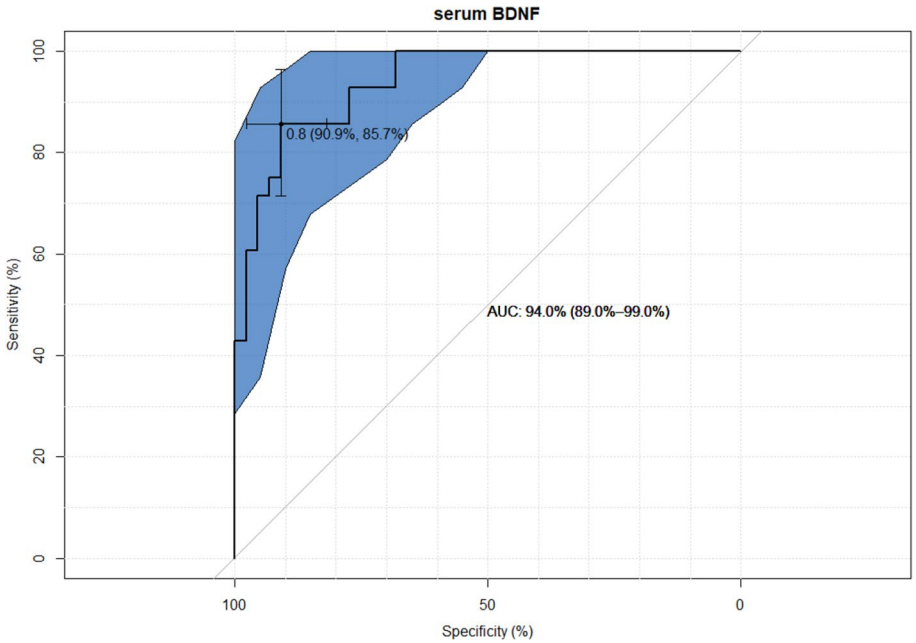

Fig. 5 The assessment of usefulness of BDNF as an CKD marker in serum (ROC curve)-study group

What is more, significant correlations between serum irisin level and SDS weight, SDS height, total protein and HCO3 levels occurred. In addition, urine irisin level correlated with SDS height and serum albumin. Another significant correlation was found between urine BDNF level and both SDS weight and SDS height. No other correlations were noted (Table 4).

Discussion

Bearing in mind the mentioned reports alongside with outcome of this research, it is assumed, that BDNF and Ir have the potential to become CKD markers. However, despite the need of new, more sensitive than serum creatinine or cystatin C, CKD markers, BDNF or Ir are mentioned in such role quite rarely [41, 42]. According to ROC curve presented in our manuscript, both BDNF and Ir meet the requirements for a good marker, regarding sensitivity and specificity. Nevertheless, CKD is a disease complicated by multiple conditions, such as malnutrition, that might considerably influence obtained results. Malnutrition in children with CKD still is a challenging clinical aspect, therefore we decided to assess potential associations between

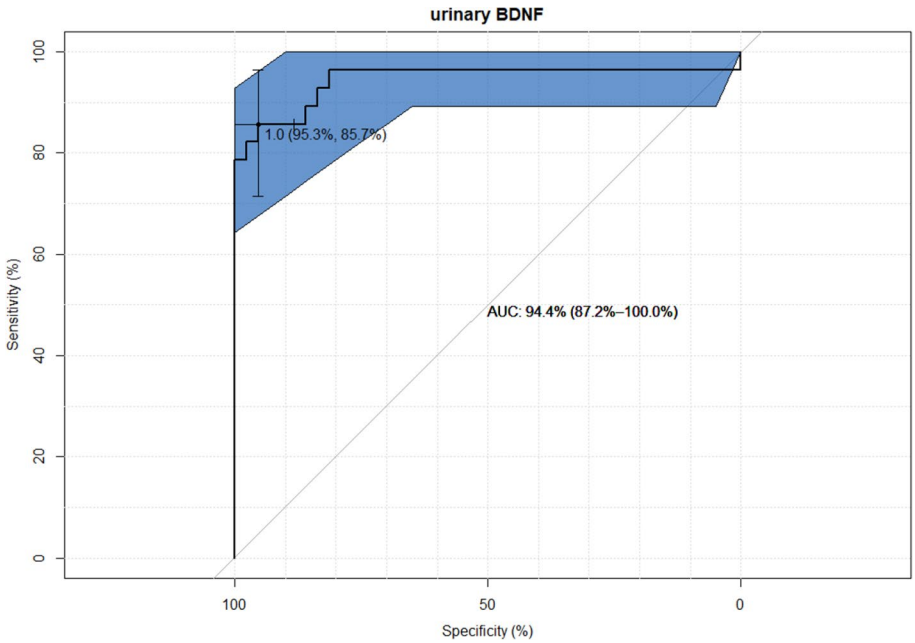

Fig. 6 The assessment of usefulness of BDNF as an CKD marker in urine (ROC curve)-study group

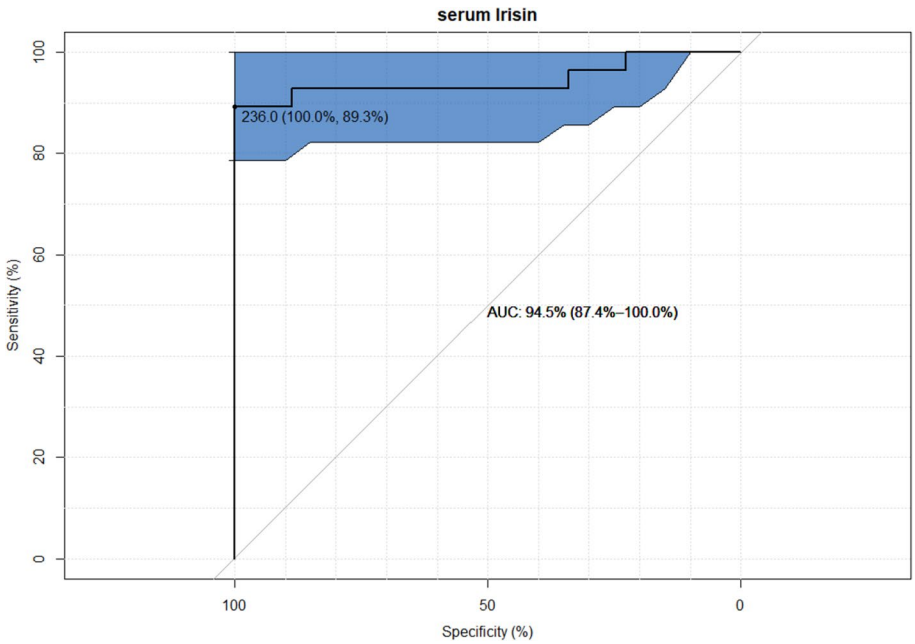

Fig. 7 The assessment of usefulness of irisin as an CKD marker in serum (ROC curve)-study group

BDNF, Ir and nutritional status among these patients. In our study, SDS weight and SDS height were notably lower in the study group compared to healthy controls. Subjective global assessment (SGA) of nutritional status was not useful for our research, as there are some data proving SGA differs with objective (anthropometry/laboratory) measurements [43].

Role of BDNF in CKD

Renal expression of BDNF is mostly described in glomeruli and tubules and is depending on podocytes' function,

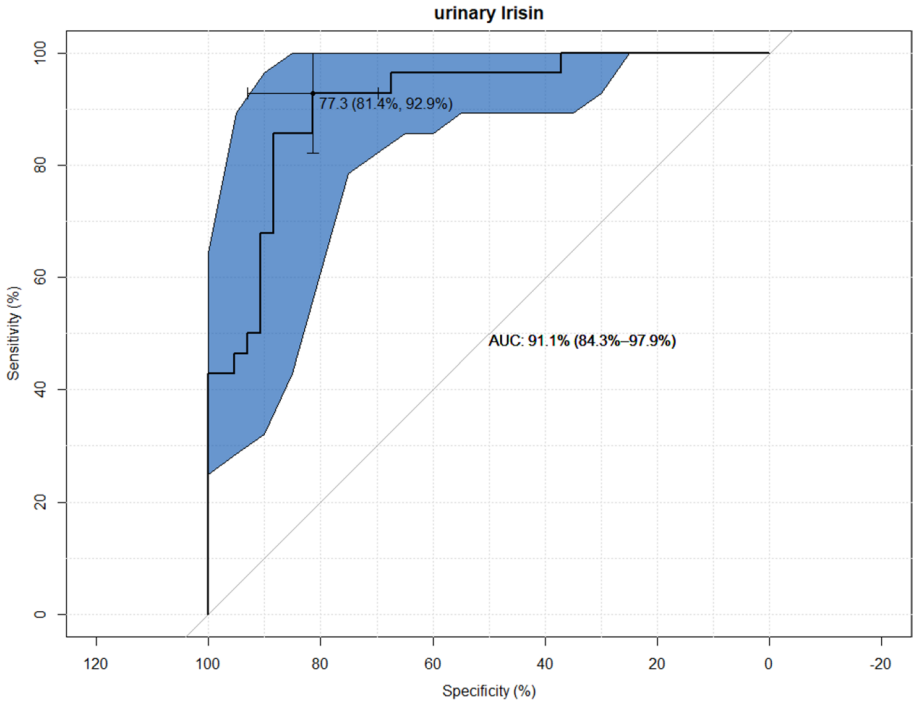

Fig. 8 The assessment of usefulness of irisin as an CKD marker in urine (ROC curve)-study group

Table 4 The relationship between BDNF and irisin serum and urine levels and height in cm, SDS height, BW (body weight) in kg, BW SDS, BMI (body mass index) in kg/m2, SDS BMI, albumin, total protein, estimated glomerular filtration rate (eGFR), creatinine, urea, uric acid, triglycerides, parathormone (PTH), hemoglobin (Hb), bicarbonate (HCO3) and high-density lipoprotein (HDL) levels, (Spearman's correlation coefficient)

Parameter	Serum BDNF		Urine BDNF		Serum irisin		Urine irisin	
	R	P	R	P	R	P	R	P
Height cm	-0,013	0,916	-0,128	0,286	0,173	0,146	0,153	0,203
Height SDS	0,172	0,147	-0,364	0,002	0,363	0,002	0,256	0,031
BW kg	-0,04	0,709	-0,091	0,453	0,145	0,226	0,097	0,42
BW SDS	0,099	0,41	-0,273	0,021	0,339	0,004	0,192	0,109
BMI kg/m2	-0,201	0,09	-0,012	0,9	0,005	1	-0,092	0,4
BMI SDS	-0,067	0,575	-0,025	0,836	0,049	0,682	-0,042	0,726
Albumin	0,064	0,746	-0,285	0,142	-0,251	0,197	0,443	0,018
Total protein	0,142	0,47	-0,065	0,743	-0,402	0,034	0,33	0,086
eGFR	-0,006	0,975	0,214	0,275	0,268	0,168	0,123	0,534
Creatinine	-0,002	0,992	-0,259	0,182	-0,244	0,211	-0,09	0,648
Urea	0,174	0,376	0,13	0,51	-0,078	0,694	-0,035	0,86
Uric acid	0,171	0,386	0,028	0,888	-0,005	0,981	-0,074	0,708
Triglycerides	-0,004	0,982	0,037	0,852	-0,041	0,836	-0,125	0,527
PTH	0,181	0,367	0,278	0,159	-0,199	0,318	-0,107	0,596
Hb	-0,164	0,403	-0,138	0,484	0,079	0,691	-0,003	0,988
HCO3	-0,169	0,389	0,103	0,601	0,48	0,01	0,048	0,809
HDL	0,325	0,151	0,039	0,867	-0,056	0,81	0,432	0,051

whereas TrkB receptor is expressed in epithelial cells of the proximal and distal tubules, as well as collecting tubules [17, 18, 44–46].

Endlich et al. proved a strong positive correlation between expression of BDNF and KIM-1 in urine cells in CKD patients, thus BDNF might be considered as a CKD marker [18]. Similar approach was presented by Afsar et al., as they suggested a correlation between serum BDNF concentrations and the occurrence of factors associated with CKD, such as sarcopenia, depression, insulin resistance, oxidative stress or inflammation. However, since the available outcomes on BDNF levels in various conditions are inconsistent, the authors highlighted the need for further studies on BDNF as a potential CKD marker [20].

BDNF is reportedly presented as a vital factor in food intake control, as well as progression of both AN and obesity, hence it occurred as a useful marker in nutritional status assessment among CKD patients [47]. Still, a variety of functions of BDNF in human body obliged us to analyze the outcome of our study considering multiorgan influence of this neurotrophin.

In our research, significanly lower serum BDNF and significalntly higher urine BDNF levels were noted in the study group. Moreover, all the parameters were characterized by good sensitivity and specificity, making a reasonable potential disease markers. We concluded, that low levels of serum and high levels of urine BDNF in the study group were a consequence of CKD complications, rather than progression of the disease, as positive correlations between serum or urine BDNF concentrations and neither serum creatinine nor urea were found. Consequently, we suggest, that BDNF should not be used as an independent marker of CKD development. Moreover, we evaluated BDNF as a malnutrition predictor by assessing the correlation between its serum and urine levels and patients' anthropometric measures. Still, significant positive correlation was found only between urine BDNF level and SDS weight and SDS height. Following on from that, patients with elevated urine BDNF levels had lower body weight and height than the average. Nevertheless, there is a need to perform further research in a larger group of participants.

AN is considered to be a well-known CKD complication, originating from imbalance in orexigenic and anorexigenic hormones, accumulation of metabolic waste, acidosis and disturbed sense of taste amplified by taken medication [9]. Anorexigenic role of BDNF was described in several studies, however the majority of research on patients with AN presented its decreased serum levels in those patients, that would most likely be a consequence of adaptive mechanisms to prevent further development of the disease [27, 47, 48]. Therefore, we suggest, that among malnourished patients with CKD a compensatory decrease in serum BDNF level might be observed, that would then stimulate increase in food intake, however such conclusions require further research.

Another vital outcome from our study showed, that patients with albuminuria exhibit lower urine BDNF concentrations. According to the literature, knowledge of albuminuria and BDNF connection is still scarce. Kurajoh et al. suggested that patients with albuminuria were at greater risk of CKD accompanied by low serum BDNF levels [21]. In above-mentioned study, Endlich et al. proved, that low urinary BDNF levels in correlation with increased albuminuria may suggest a possible BDNF impact on glomerular filtration barrier function [18]. A different approach was presented by Badeński et al., as they implied, that patients with INS, presenting proteinuria and albuminuria, had BDNF levels decreased in serum and elevated in urine, presumably due to podocyte damage [17]. Since there are some inconsistencies in recent data regarding the relation between albuminuria and BDNF, further research is required in this filed.

Regardless a number of reports confirming a decrease in BDNF concentration in CKD, Shin et al. proved, that serum BDNF levels are elevated in patients undergoing hemodialysis, compared to healthy controls [49]. We believe, that data presented by Shin et al. could be a result of secreting BDNF by platelets, activated during hemodialysis, by a contact with dialysis membrane [47, 49–51]. Considering the outcome presented by Shin et al. we decided to include patients in pre-dialysis into our research, even though dialysis is a factor mainly leading to malnutrition. Nevertheless, it is desirable to include dialysis patients to such study in the future as well.

Role of irisin in CKD

Our attention was drawn towards some studies, which found the connection between Ir concentration and CKD stage. Ebert et al. conducted a research on 532 patients with CKD and proved, that Ir levels were dropping together with increasing stage of the disease. According to the authors, unlike other adipokines and various metabolic hormones, Ir does not show renal clearance, hence its serum concentration in advanced stages of CKD decreased. A study by Ebert et al. however did not include urine Ir levels, which, in our opinion, is a minor limitation [39]. The outcome of our research shows a correlation between low serum and low urine Ir levels; therefore, we assume, that Ir indeed shows renal clearance, but independent of CKD stage.

Meta-analysis performer by Gan et al., including the above-mentioned studies, concluded, that Ir concentration is decreased in CKD patients, particularly in those undergoing dialysis [35]. Main factors, suspected to

influence dialysis patients, were reduced physical activity and malnutrition [35]. Shad et al. confirmed the impact of CKD progression on Ir level, as its lower concentrations were observed in patients in 4th stage, comparing to a group in 2nd stage of CKD [38]. Similar conclusions were reached by Wen et al., who presented significantly lower serum Ir levels in adults with CKD, compared to healthy controls as well as a negative correlation of Ir and both urea and serum creatinine. Lower muscle mass and reduced physical activity were considered to be inducing Ir level elevation in this group [52].

According to literature, there is a positive correlation between the Ir level and body weight as well as body mass index (BMI). Therefore, we decided to evaluate correlations between this adipomyokine and nutritional status in children with CKD [53–55].

Our study showed significantly lower serum and urine Ir levels in CKD patients, compared with control group. However, neither eGFR nor urea correlated positively with those Ir concentrations. Patients with lower body weight and shorter stature had decreased Ir levels and it correlated positively with HCO3. Surprisingly, serum Ir levels decreased in inverse proportion to the serum total protein, although we anticipated lower protein concentrations due to malnutrition. Nevertheless, serum total protein was below lower limit of normal in none of our participants, despite low body weight and short stature. On the other hand, urine Ir levels were dropping together with serum albumin decrease and height lower than the average.

Moreover, Wen et al. presented Ir as a promising therapeutic agent for cardiovascular disease in CKD patients, as its levels were independently correlated with high-density lipoprotein cholesterol (HDL) [52]. In this manuscript we would like to present similar conclusions, however, in our research, the correlation between Ir and HDL was not statistically significant (p=0,051).

We suggest, as mentioned before about BDNF, that our outcome shows a potential impact of Ir on assessing CKD complications, particularly malnutrition, not progression of CKD per se. The knowledge of Ir influence on malnutrition or cachexia development is still scarce. It is believed, that Ir has a potential to restore muscle tissue damaged by oxidative stress, also caused by aging [56].

Homa-Mlak et al. performed their study on patients suffering from head and neck cancers (HNC) and concluded, that this group, being at high risk of malnutrition, according to Nutritional Risk Score 2002 (NRS 2002) and SGA, reached higher Ir levels in comparison with healthy controls. They did not find a statistical correlation between Ir level and objective parameters, such as BMI. According to their hypothesis, Ir induced WAT to BAT conversion could lead to malnutrition [57, 58]. A potential Ir role in nutritional status assessment among patients with CKD was also described by Kałużna et al., as they proved the occurrence of lower Ir concentrations in ESRD. However, in oppose to this article, no correlation with anthropometric measures was presented [59]. We believe, that the level of both serum and urine Ir might be a potential marker of malnutrition in CKD, however further research on this topic is required.

Still, our study has some limitations. Considerably small study group kept us from analyzing stages of CKD separately. Moreover, we had to resign from studying the bioelectrical impedance analysis (BIA) outcome, as some of the participants did not meet age criteria. We also did not use any anthropometric methods to evaluate muscle mass, since no objective methods to perform such investigation are available for polish pediatric population.

Conclusions

Considering obtained outcome and regarding multifaceted role of BDNF in CKD, we believe, that it could not serve as an independent marker, but might be a part of a group of parameters evaluating the risk factors of CKD progression in children. Moreover, we would like to highlight the need to conduct research on this topic on a larger group of participants, including dialysis patients. Such study might show if fluctuation in BDNF and Ir concentrations arise from kidney function deterioration or are a consequence of nutrition disorders or other complications of CKD. Currently used biochemical parameters do not bring any benefits in nutritional status assessment. Therefore new, more sensitive markers, that would indicate a group of patients at greater risk of malnutrition or PEW, are desirable. According to our research, urine BDNF and both serum and urine Ir levels might become a useful marker of malnutrition, what requires more detailed investigation.

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Authors' contributions
Author Contributions: Conceptualization, A.G.,M.B.,M.D. and M.S.; Data curation A.G.,E.Ś.,M.D.,O.B.; Methodology, A.G.,E.Ś.; Formal analysis, A.G.,M.D.; Project administration, A.G , Resources A.G and M.S.; writing-original draft preparation, A.G.,M.B. and E.T.-D.; Writing-review and editing A.G.,M.B.,A.B.,M.S.; Visualization, O.B.; Supervision, A.M.-K. and M.S.; Validation, A.M.-K. and M.S. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy issues.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Medical University of Silesia in Katowice (KNW/0022/KB1/31/I/19, 14.05.2019). Informed consent was obtained from all subjects involved in the study. Informed consent was obtained from legal guardians where necessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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