ARTICLE

Serum Adiponectin Level in Children with Nephrotic Syndrome in Relation to Right Ventricular Functions and Metabolic Profiles

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Abstract

Background: Adiponectin (ADPN), a protein hormone (cytokine), is exclusively expressed on and secreted from adipocytes. It is a particularly interesting compound because it may have a protective influence on the cardiovascular system. **Objective:** This study was designed to evaluate serum ADPN level, right ventricular functions and metabolic profiles among children with nephrotic syndrome (NS) and asses the correlations between ADPN as a protective hormone and each of right ventricular functions and metabolic profiles. **Patients and Methods:** A total of 47 children (28 boys; 19 girls) with steroid-responsive nephrotic syndrome (SRNS) were studied. They included two groups: Group A: included 25 children with SRNS in relapse. Group B: included 22 children with SRNS in remission for periods ranging from 3-9 months. A control group included 28 children with matched age and sex. Methods: Serum level of ADPN was estimated by ELISA and nitric oxide (NO) by chemical detection. In addition to total cholesterol, triglycerides, high-density lipoprotein (HDL), low density lipoprotein (LDL), total protein, and albumin by Enzymatic Colorimetric kits. Also, 24-hour urine samples were collected for detection of proteinuria. Electrocardiogram (ECG) and echocardiography measuring right ventricular wall functions were done. **Results:** Serum levels of ADPN and NO were significantly higher in children with SRNS in relapse in comparison with children with SRNS in remission or control group. Children with SRNS in relapse showed significantly higher levels of total cholesterol, triglycerides, LDL and proteinuria while significantly lower levels of total protein, albumin and HDL as compared with SRNS in remission or control group. Echocardiographic findings revealed that a significant decrease in right ventricular ejection fraction (RVEF %) and significant increase in right ventricular end diastolic diameter (RVEDD), right ventricular peak pressure (RVPP) and pulmonary artery pressure (PAP) were found in cases with SRNS in relapse in comparison to cases with SRNS in remission and control

group. ECG findings were indicative for right ventricular hypertrophy in relapsed cases. Finally, in children with SRNS in relapse it was found that serum ADPN level was significantly positively correlated with each of serum NO, total cholesterol, triglycerides, LDL, proteinuria, RVEDD, RVPP and PAP, while significantly negatively correlated with serum total protein, albumin and RVEF%.

Conclusion: During relapse of SRNS, serum ADPN level is higher than its level in SRNS in remission. This higher level may represent a physiologic response to the altered metabolic profiles and right ventricular strain so as to minimize cardiovascular complications.

Keyword: Adiponectin, Nephrotic syndrome, Right ventricular function, Nitric oxide proteinuria.

Introduction

Adiponectin (ADPN), a protein hormone is exclusively expressed in and secreted from adipocyte (1). Receptors for this protein (i.e. Adipo-R1 and Adipo-R2) are present in most organs (2). ADPN is primarily involved in the regulation of lipid and glucose metabolism by increasing fat oxidation and insulin sensitivity (3). In addition, it is a particularly interesting compound because it may have a protective influence on the cardiovascular system. It suppresses the attachment of monocytes to endothelial cells and modulates the endothelial response to inflammatory stimuli (4). The potential protective role of ADPN in human diseases is supported by the observation that plasma ADPN is low in patients with coronary artery diseases and in patients with type 2 diabetes mellitus (5). ADPN serum level has been suggested as a useful predictive marker of cardiovascular diseases in patients with chronic renal diseases who are not on dialysis (6,7). Nephrotic syndrome (NS) is a high risk disorder as unabated urinary protein lossleads to hypoalbuminemia, hyperfibrinogenemia and hypercholesterolemia independent of renal function (8). Multiple factors raise concerns for cardiovascular sequela with long term NS: involving exposure to corticosteroid, hyperlipidemia, oxidative stress, hypertension, hypercoagulability and anaemia (9). Although thromboemolism may occur anywhere, deep venous thrombosis and pulmonary embolism are the most frequently encountered manifestations in the clinical setting and may be correlated to right ventricular function (10). Dyslipoproteinemia is probably responsible for endothelial dysfunction in the conduit arteries in patients with nephrosis and could be the basis for the increased risk of cardiovascular diseases in these patients (11). To our knowledge, data on ADPN level in relation to ventricular functions and metabolic profiles are limited. Therefore, we aimed to evaluate serum ADPN level and right ventricular functions in children with NS and examine the correlation between ADPN level and each of right ventricular functions and metabolic profiles.

Patients and Methods

Study Protocol

Forty-seven children with SRNS (28 males and 19 females) were included in the study and were recruited from Paediatric Department in cooperation Physiology Department, Faculty of Medicine, Assiut University. Assiut University Ethics Scientific Committee approved the work and an informed assent was obtained from the parents of children. Twenty five of them were in relapse (group A) and 22 in remission for periods between 3 and 9 months and on no corticosteroid therapy (group B) . In addition, the study included 28 children with matched age and sex as a control group (group C). Diagnosis of NS was based on heavy proteinuria (greater than or equal to 40 mg/m^2/hour), hypoalbuminemia (< 2.5 g/dl), hyperlipedemia and generalized oedema (12). Patients with hypertension, macroscopic haematuria, or abnormal renal function were excluded from the study.

Laboratory methods

Blood samples were collected after an overnight fasting (10 hours). Serum samples were stored at – 30 until analysis. Levels of ADPN were measured by ELISA method using a commercially available kit (ALPCO diagnostic, NH, USA). Serum total proteins, albumin, and protein in urine were estimated by Colorimetric assay. Serum total cholesterol, triglycerides, HDL and LDL, were estimated by Enzymatic Colorimetric Stanbio-Liquicolor kit. In addition, serum NO levels were measured chemically using Griess reagent according to the method of Ding et al (13).

Echocardiographic and Doppler Studies

Right ventricular functions were evaluated by echocardiography using Vivid 3, Aloka machines with transducers of 3.5, 7 MHz. Cases who were discovered to have congenital heart disease, rheumatic heart disease or other known cardiac abnormalities were excluded from the study. We used different echocardiography Modes: 1) Two dimensional (2D) to verify cardiac chambers structures and details of anatomy. 2) M mode was used to estimate the following: Right ventricular end diastolic diameter (RVEDD), Right ventricular peak pressure (RVPP), Right ventricular ejection fraction (RVEF%) according to the criteria of the

American Society of Echocardiography (14). Doppler and colour Doppler study were used to detect pulmonary artery pressure (PAP) (15). Also, twelve-lead electrocardiograph (ECG) was recorded.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for all parameters. The data were analysed using GraphPad Prism data analysis program (GraphPad Software, Inc., San Diego, CA, USA). For the comparison of statistical significance between cases and control, Student Newman-Keuls t-test for unpaired data was used. Correlations of ADPN levels with other variable were assessed using Spearman's non-parametric correlation coefficient according to that described previously (16). A value of $P < 0.05$ was considered statistically significant.

Results

Metabolic Profiles

Metabolic profiles of the studied groups are shown in Table 1. Cases with NS in relapse (group A) have significantly higher levels of serum total cholesterol, triglycerides, LDL protienuria, and significantly lower levels of total protein, albumin (with $P<0.001$ for each) and HDL ($P<0.05$) in comparison with cases in remission (group B) or control group (group C). Serum ADPN and NO level were significantly higher ($P<0.001$ for each) in group A as compared with group B and C. Values of this parameter were non-significantly varied among group B and group C.

Table 1. Metabolic profiles of the three study groups (A,B & C) and the significance of differences between them

	SRNS in relapse n =25 Group (A)	SRNS in remission n =22 Group (B)	Control group n =28 Group (C)	Significance		
				A vs. B	A vs. C	B vs. C
Total Protein (g/dl)	3.9±0.6	6.7±0.4	6.8±0.7	***	***	NS
Albumin (g/dl)	1.9±0.3	4.3±0.3	4.2±0.4	***	***	NS
Cholesterol (mg/dl)	415±1	143±3	134±2	***	***	NS
Triglyceride (mg/dl)	255±6	132±3	133±2	***	***	NS
HDL Cholesterol (mg/dl)	46±7	52±9	56±9	*	*	NS
LDL Cholesterol (mg/dl)	215±4	67±2	62±1	***	***	NS
Nitric Oxide (μmol/L)	7.5±0.9	4.2±0.8	3.8±0.7	***	***	NS
Urinary Protein Excretion (g/24 hours)	7.9±1.0	0.1±0.0	-	***	-	-
ADPN (μg/ml)	33.4±9.5	12.5±6.3	10.6±4.6	***	***	NS

SRNS: steroid responsive nephrotic syndrome, HDL: high density lipoprotein, LDL: low density lipoprotein, NO: nitric oxide, ADPN: adiponectin * : $P < 0.05$, *** : $P < 0.001$. NS: non significant. vs: versus. Data are presented as means ± SD.

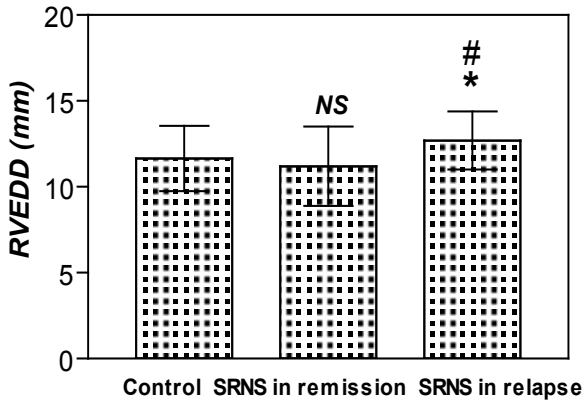

Figure 1. Right ventricular end diastolic diameter (RVEDD) mm, in the studied groups. * : P<0.05 as compared to control # : P < 0.05 as compared to SRNS in remission, NS: non significant as compared to control.

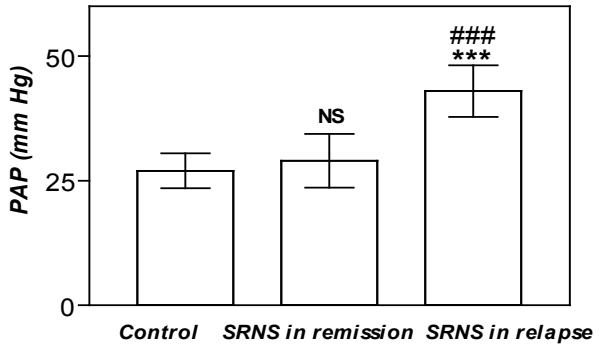

Figure 3. Pulmonary artery pressure (PAP) mmHg, in the studied groups. *** : P< 0.001 as compared to control, ### : P < 0.001 as compared to SRNS in remission, NS: non significant as compared to control. Data are expressed as means ± *SD.*

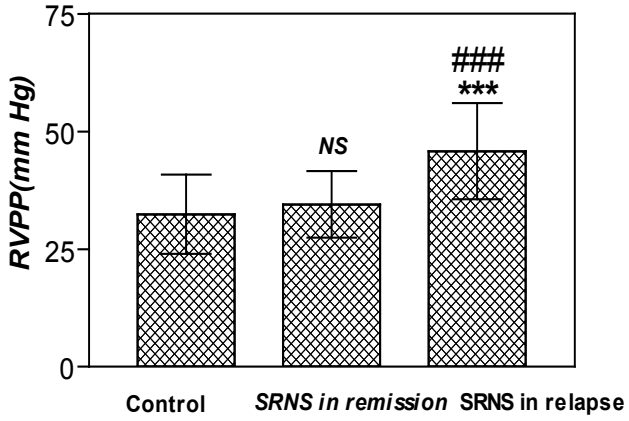

Figure 2. Right ventricular peak pressure (RVPP) mmHg, in the studied groups.*** : P< 0.001 as compared to control, ### : P < 0.001 as compared to SRNS in remission, NS: non significant as compared to control.

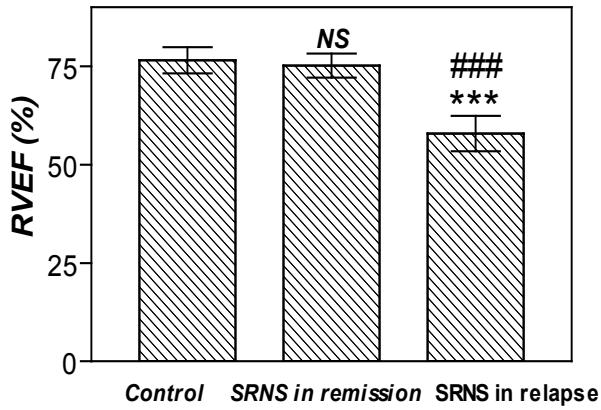

Figure 4. Right ventricular ejection fraction (RVEF %) in the studied groups. *** : P< 0.001 as compared to control, ### : P < 0.001 as compared to SRNS in remission, NS: non significant as compared to control. Data are expressed as means ± SD.

Echocardiograghic and ECG Findings

Figures (1-4) show echocardiographic data of the studied groups: Right ventricular end diastolic diameter (RVEDD), right ventricular peak pressure (RVPP) and pulmonary artery pressure (PAP) were significantly higher (P<0.05 for RVEDD, P<0.001 for RVPP and for PAP) while right ventricular ejection fraction (RVEF%) was significantly lower (P<0.001) among cases in relapse than in cases in remission or control group. Values of these parameters were non-significantly varied among remission and control group. ECG findings of relapsed children were indicative for right ventricular hypertrophy and were shown in table 2, 60% of them had high voltage of R wave in leads V_3R-V_4R and deep S wave in lead I. Forty percent had positive T wave in leads V_3R-V_4R and V_1-V_3. ECG findings in patients with remission were normal.

Correlation Analysis

Table 3 shows correlation coefficients between serum ADPN level and each of metabolic profiles and right ventricular function measurements among cases with relapse. Serum ADPN levels have significant positive correlations with each of total cholesterol (r =0.765, P<0.001), triglycerides (r= 0.604, P<0.001), LDL (r =0.678, P<0.001), NO (r=0.815, P<0.001), proteinuria (r=0.653, P<0.001), RVEDD (r=0.512, P<0.01), RVPP (r=0.862, P<0.001)

Table 2. ECG findings in SRNS relapsed patients		
ECG Findings	Number of patients	Percent
High voltage of R wave in leads V_3R-V_4R and deep S wave in lead I.	15	60%
Positive T wave in leads V_3R-V_4R and V_1-V_3.	10	40%

Table 3. Correlation coefficient between ADPN level and each of metabolic profiles and echocardiographic data among cases in relapse			
Parameters		r	p
Metabolic	Total Plasma proteins	- 0.708	< 0.001
	Plasma Albumin	- 0.833	< 0.001
	Total Cholesterol	0.765	< 0.001
	Triglycerides	0.604	< 0.001
	LDL Cholesterol	0.678	< 0.001
	NO	0.815	< 0.001
	Urinary Protein Excretion	0.653	< 0.001
Echocardiographic	RVEDD	0.512	< 0.01
	RVPP	0.862	< 0.001
	PAP	0.761	< 0.001
	RVEF %	- 0.615	< 0.001

ADPN: adiponectin, NO: nitric oxide, LDL: low density lipoprotein, RVEDD: right ventricular end diastolic diameter, RVPP: right ventricular peak pressure, PAP: pulmonary artery pressure, RVEF: right ventricular ejection fraction

and PAP (r=0.761, P<0.001), while have significant –ve correlations with each of serum total protein (r= - 0.708, P<0.001), albumin (r = - 0.833, P<0.001) and RVEF% (r= - 0.615, P<0.001).

Discussion

Steroid responsive NS is one of the commonest renal diseases in childhood. Unfortunately, around 60% of steroid responsive patients experience five or more relapses (17). Medical complications of NS are potentially serious. They can be divided into two major subgroups: acute complications related to the nephrotic state especially infections and thromboembolic disease and long term sequela of NS and its treatment especially effects on bone, growth and the cardiovascular system (18). Multiple factors raise concerns for cardiovascular sequela in children with long term NS including hyperlipdemia, oxidative stress, hypertension, hypercoagulability, anaemia and exposure to steroid (9).

In the present study, serum ADPN level was significantly higher in cases with SRNS in relapse in comparison with cases in remission or control group. These results are in agreement with those of Bakkaloglu et al (1) who found that SRNS relapsed patients had substantially higher ADPN level compared to those in SRNS remission and control

group. Our results are also in agreement with those of Guebre-Egziabber et al., (19) who reported a significant increase of ADPN in chronic renal diseases in comparison with control.

The mechanism of the elevated serum ADPN levels in NS remains unclear. Zaccali et al (8) speculated that proteinuria besides triggering profound metabolic changes leading to hyperlipdemia in the liver, also triggers a parallel increase in ADPN synthesis in the fat cell. Previous reports (20-22) found that patients with advanced diabetic nephropathy have elevated circulating ADPN levels despite increased urinary ADPN levels. They speculated that ADPN synthesis in adipose tissue might be enhanced to mitigate microvascular damage in the advanced stages of diabetic nephropathy. Also, Bakkaloglu et al (1) speculated that a rise of serum ADPN levels in SRNS patients may be a compensatory response resulting mainly from proteinuria and related plasma lipid abnormalities in order to prevent harmful and deleterious complications of NS. The previous suggestions are confirmed by the results of the present study where direct correlations were present between ADPN and each of cholesterol; triglyceride, LDL and protineuria while significant inverse correlations were found between ADPN and total plasma proteins and albumin. In addition, recent studies (23, 24) reported that the high ADPN associated with more severe proteinuria in chronic kidney disease patients, is possibly a protective response aimed at countering the high renal and cardiovascular risk of high proteinuria.

It has been shown that, patients with NS have a considerable degree of endothelial dysfunction (25). Previous studies found that the mechanism by which ADPN exerts vasculoprotective effect is through its direct actions in the vascular system by stimulating endothelial NO production from vascular endothelium, thus improve endothelium-dependant vasodilatation (26-28). In line with these data, this study showed that serum NO level was significantly increased in cases with SRNS in relapse as compared to cases with SRNS in remission or control group and that ADPN level is directly related to NO in SRNS in relapse (significant positive correlation).

In the present study, aiming for evaluation of the right ventricular functions in NS, we found a significant decrease in RVEF % in cases with SRNS in relapse as compared to cases with SRNS in remission and controls. The RVEDD, RVPP and PAP were significantly increased in relapsed cases in comparison with both remission cases and controls. These results are similar to the results of Qin et al (29) who found a significant difference between patients with early onset and relapsed NS and controls regarding RVEF% and RVPP. But in contrast to our results, they found no significant difference in RVEDD between patients with NS (early onset and relapsed) and controls.

In the present study, it is noteworthy that abnormal ECG findings were observed in cases with SRNS in relapse. Sixty percent of them had high voltage of R wave in leads V_3R-V_4R and deep S wave in lead I. and 40% had positive T wave in leads V_3R- V_4R and V_1-V_3. This is suggestive of right ventricular hypertrophy and most probably due to pulmonary arterial hypertension (PAP). PAP was significantly higher in relapsed SRNS in comparison to cases in remission or controls. An association of pulmonary hypertension and nephrotic syndrome was reported previously (31,32) referred to hypoxia and increased glomerular size in a maladaptive compensatory mechanism. During this phase, a maladaptive right ventricular hypertrophy and variable degrees of interstitial fibrosis take place leading to an altered right ventricular diastolic pressure-volume relationship and increased RVPP. With persistent pressure overload, the right ventricle undergoes a remodelling process. Eventually the right ventricular chamber dilates and increased wall stress leading to increased oxygen consumption in right ventricular myocardium. This would lead to right ventricular ischemia and dysfunction. Therefore, the aetiologies of right ventricular dysfunction in children with NS could be ascribed to the following: firstly, impaired functional reserve by hemodynamic stress. Secondly, the elevated RVPP and RVEDD which could be caused by pulmonary arterial hypertension (29,32).

It was reported previously that ADPN is synthesized and secreted by isolated murine and human cardiomyocytes, and was suggested that local production of this hormone by cardiomyocytes could be involved in the regulation of cardiac metabolism and function (33,34). The authors also showed that ADPN-promoted enhancement of glucose uptake by cardiomyocytes might be mediated by activation of adenosine monophosphate-activated protein kinase (AMPK) pathway (as it is in adipocytes). Another study found that pressure overload in ADPN-deficient mice resulted in enhanced concentric cardiac hypertrophy. Administration of ADPN attenuated and inhibited hypertrophic signalling in the myocardium of these animals by activating AMPK pathway (35). Accordingly, in our study it is possible that the increased circulatory ADPN in cases with SRNS in re-

lapse might be due to local production by cardiomyocytes as well as by adipocytes as a counteracting mechanism to compensate for right ventricular hypertrophy.

Regarding the correlations between right ventricular dysfunction and ADPN level, the present study found a significant inverse relationship between ADPN and RVEF% and significant direct correlations between ADPN and each of RVEDD, RVPP and PAP. Are these correlations a mere statistical findings or do they have biological basis? Our explanation is that increased secretion of ADPN confers a reactive and protective response to a heightened cardiovascular strain in NS.

During relapse of SRNS, serum ADPN level is higher than its level in SRNS in remission, which may represent a physiologic response to the altered metabolic profiles and right ventricular strain so as to minimize cardiovascular complication.

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