Serum visfatin, ferritin and lipid Atherogenic risk ratios as predictors of cardiovascular diseases in end stage renal disease patients

HANAN MAHMOUD FAYED[1], MONA MOHAMMED ABDELMEGUID[2], SAMAR SAYED AHMED[3], MOSTAFA MOHY AMER AMER[2]

[1]Department of Clinical and Chemical Pathology, Qena Faculty of Medicine, South Valley University, Qena, Egypt; [2] Department of Clinical and Chemical Pathology, Azhar Assuit Faculty of Medicine, Azhar University, Assuit, Egypt; [3]Department of Community Medicine, Qena Faculty of Medicine, South Valley University, Qena, Egypt

Received 12 January 2017
Accepted 22 February 2017

ABSTRACT

Objective: The aim of this work was to evaluate serum visfatin, ferritin, and lipids as predictors of cardiovascular diseases (CVD) in end-stage renal disease (ESRD) patients.

Methods: A controlled trial involving thirty ESRD patients on maintenance haemodialysis (HD); serum was assayed for urea, creatinine, glucose, lipid profile, ferritin and visfatin.

Results: patients aged (57.67±5.59 years); 11(36.6 %) were diabetics and 19(63.3%) non-diabetics; 14(46.7%) men and 16(53.3%) women with mean duration of therapy (5.45±2.9 years). Patients have high serum urea, creatinine, non-HDL, TG, LDL-c, VLDL, visfatin, and ferritin (P<0.001) and the calculated risk ratios were high (P<0.001) (VLDL/HDL, non-HDL/HDL, cholesterol/HDL, LDL/HDL, TG/HDL). BMI (P=0.006), weight (P=0.016), HDL-c (P=0.009), glucose (P=0.001, HbA1c (P=0.014) and LDL/VLDL (P=0.045). Visfatin correlated with; BMI (r=0.82, P<0.001), both cholesterol and non-HDL (r=0.98, P<0.001), VLDL/HDL (r=0.49, P=0.006), non-HDL/HDL (r=0. 86, P<0.001), cholesterol/HDL (r=0.85, P<0.001), LDL/HDL (r=0.51, P=0.004), TG/HDL (r=0.47, P=0.009) and inversely correlation with HDL-c (r=-0.85, P<0.001). Ferritin; showed inverse correlation with diastolic BP (r=-0.559, P=0.001). Multiple linear stepwise regression analysis confirmed three ratios to be significantly contributing to the risk of CVD in ESRD-HD patients (total cholesterol/HDL, LDL/HDL, and TG/HDL); while VLDL/HDL, not a risk factor. Logistic regression revealed that the risk of CVD is associated with BMI, TG, non-HDL, LDLC, VLDL, urea, glucose, HbA1c and ferritin.

Conclusion: Dyslipidemia, hyper-visfatinaemia, and hyper-ferritinemia were prevalent in the ESRD-HD patient's all of which are independent risk factors for CVD; using atherogenic risk ratios as a screening tool for the estimation of CVD risk is useful in those patients

KEY WORDS: Lipid profile
Visfatin
Ferritin
Atherogenic risk ratios
End stage renal disease

Introduction

Cardiovascular diseases (CVD) remain the major cause of morbidity and mortality in chronic kidney disease (CKD) patients. Traditional CV risk factors including dyslipidemia, hypertension, diabetes mellitus (DM) and smoking are highly prevalent in those patients. Non-traditional biomarkers e.g. markers of inflammation, oxidative stress (OS) and endothelial dysfunction were associated with increased CVD and mortality risk in population with and without CKD [1]. Progression of CKD is associated with decreased endothelial function and increased prevalence of atherosclerosis, all of which was associated with mortality [2]. Dyslipidemia is an independent risk factor implicated in increased CVD and deaths associated with CKD and in the progression of renal damage [3].

Visfatin; a nicotinamide phosphoribosyl transferase (Nampt) plays a pivotal role as regulator of cell energy balance as it modulates lipid and glucose metabolism and insulin sensitivity [4]. Visfatin have multiple biological functions as an autocrine, endocrine and paracrine peptide; found in cells in many tissues and organs (both the nucleus and the cytoplasm) but preferentially expressed in visceral adipose tissue [5].

Correspondence to: Dr. Hanan Mahmoud Fayed
Email: hananfayed@yahoo.com

It is also produced by a variety of cells including lymphocytes, monocytes, neutrophils and hepatocyte. Increased levels of visfatin are found in both acute and chronic inflammatory diseases [6]. Many observations suggested a direct association between endothelial dysfunction and visfatin levels e.g. type 2 DM and CKD, a positive correlation has been reported between visfatin levels and several markers of systemic inflammation and endothelial dysfunction [7]. Furthermore; endothelial dysfunction was an early and essential step in the evolution of the atherosclerotic process [8]. Visfatin is also known as pre–B-cell colony-enhancing factor 1 that enhances the activation of leukocytes, synthesis of adhesion molecules and production of pro-inflammatory cytokines e.g. interleukin-6 (IL-6) and TNF-α [9]. IL-6 stimulates hepatocytes to produce various pro-inflammatory cytokines and IL-6 stimulates transcription of CRP and hepcidin which regulates both iron absorption (by enterocytes) and release (by macrophages); decreased hepcidin levels lead to increased iron absorption [10]. Iron is linked to OS as it contributes in the formation of free radicals which induce lipid peroxidation [11]. OS induces both insulin resistance and increased ferritin synthesis [12]. Fernández-Real et al. [13] found that iron influences glucose metabolism, even in absence of iron overload and Iwasaki et al. established that serum ferritin was significantly associated with the degree of insulin resistance, visceral fat and hepatic fat content. Similar to serum ferritin; visfatin was found to be increased in type 2 DM [15], therefore factors related to OS or hyperglycemia can mediate the association between visfatin and prohepcidin (an iron metabolism parameters) in subjects with altered glucose tolerance [16]. Ferritin, a clinical marker of iron storage, is also an acute-phase reactant that induces macrophage accumulation and increases reactive oxygen species formation, so if inflammation is prolonged with a chronic acute-phase reaction, adverse outcomes such as endothelial damage and atherosclerosis may occur [17-18]. In dialysis patients; hyperferritinemia indicate erythropoietin resistance, malnutrition or inflammatory status [19-20]. Hyperferritinemia was associated with high poor clinical outcome and mortality [21]. Therefore; the aim of this study was to evaluate the relationship between serum adipocytokine visfatin, ferritin and lipids cardiovascular risk ratios among ESRD patients on regular HD.

Materials and methods

Study design and subjects: A controlled clinical trial including thirty patients with ESRD on maintenance HD (for at least one year) attending nephrology unit of Luxor general hospital, Luxor- Egypt. All patients received HD 3 times/week, each for 4 hour, using bicarbonate dialysis solution with polysulphone membrane. Twenty healthy volunteer free of features of kidney disease and having a normal blood urea and serum creatinine level and estimated GFR > 90 ml/min/1.73 m^2 were selected as control. The study was conducted after approval by ethical committee in Qena Faculty of medicine and informed consent was taken from all the participants and all the experiments were strictly adhered to the tenets of the Helsinki declaration.

Exclusion criteria

Patients with history of CVD (defined as a history of heart failure, acute or chronic ischemic heart disease, and cerebrovascular disease); or CKD with recent febrile or infectious episodes, hospitalization during the past month, individuals younger than 19 years of age, pregnancy, or who take any lipid-lowering medications or antioxidant supplements or known histories of autoimmune disease, malignancy, hematological disorders, HBV or HCV and HIV or who had not fasted (for 12 hrs.) prior to blood sampling or refuse to participate in the study. Other relevant data included the cause of renal failure, duration of dialysis, presence of co-morbid factors, smoking history and hyperparathyroidism. The following characteristics were observed: age, gender, history, duration and the cause of nephropathy, medication taken by the patient, weight, height and blood pressure was measured using standard mercury sphygmomanometer. The average of two blood pressure readings, recorded at an interval of 5 min, was used for analysis.

Blood samples

5ml blood samples were taken from HD patients immediately before dialysis sessions from the dialysis fistula and from the venipuncture in control subjects after an overnight 12 hr. fast (2 ml will be taken in EDTA tube and the 3 ml in plain tube left to clot and serum is separated and aliquoted for chemistry analysis and rest put in cryo tube and preserved at -80ºC till time of analysis of visfatin).

- EDTA anticoagulant tube was used for complete cell

count using automated cell counter cell dyne-1800 (Abbott diagnostics, USA) and for HbA1c estimation.

- Plain tube centrifuged at 3000 rpm for 10 minutes and serum obtained used for measurement of biochemical parameters (urea, creatinine, glucose and serum Lipid profile including: Cholesterol, HDL-c, LDL-c, Triglycerides). All were measured by enzymatic colorimetric methods using Cobas c311 automated chemistry analyzer (Roche diagnostics, Germany).
- Serum ferritin tested as instructed by the manufacturers using commercial automated chemiluminescent microparticle immunoassay (CMIA) provided by (Architect i2000, Abbott diagnostics, USA). Serum ferritin was considered raised according to the WHO criteria if > 300 ng/mL in men and > 200 ng/mL in women, iron deficiency (ferritin <200 ng/ml), iron overload (ferritin >2000 ng/ml). Hence, these ranges of serum ferritin values are less likely to correlate with inflammation and/or malnutrition. Therefore, a sub-analysis performed in which only patients with serum ferritin values between 200 and 2000 ng/ml were analyzed.
- Serum visfatin was measured using EIA kit from WKEA MED SUPPLIES CORP; Changchun, China Catalog No: WH-1525 according to the manufacturer's instruction. The assay range: 1μg/L -20μg/L, intra assay coefficient variation (CV) <15% with a sensitivity of 0.3 μg/L.

Many calculations were assessed including:

- Body mass index (BMI): weight in kilograms divided by height in meter square, and obesity was defined as a BMI > 25 kg/m^2
- Estimated low density lipoprotein cholesterol (LDL-C) = total cholesterol (TC) – [(HDL-C) + (VLDL-C)] =TC – [HDL-C+ (Triglycerids/5)] mg/dl [22].
- Non-high-density lipoprotein cholesterol (Non-HDL) = the difference between TC and HDL-C [accounts for LDL-C, VLDL and its remnants that reflects the increased risk of coronary heart disease].
- Atherogenic ratios: total cholesterol/HDL, LDL/HDL, VLDL/HDL, Non-HDL/HDL, TG/HDL, LDL/VLDL.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM SPSS statistics; USA). Data are expressed in mean and standard deviation (mean ± SD) or median and range, according to their distribution. A parametric or non-parametric test was used for comparison of data. The distribution of variables was compared by the Chi-square test analysis. Difference between the arithmetical averages was assessed by ANOVA, which was adjusted for multiple comparisons. ANOVA with post-hoc Tukey's range test was used to compare all possible pairs of means. Depending on the normality of distribution of variables, the comparisons between groups were performed using one way of analysis of variance (ANOVA) or the Mann-Whitney U-test when results are non-parametrically distributed. Logistic Regression (Odd's Ratio) was performed for calculation of cardiac risk factors for heart attack in HD cases. All statistical tests were two tailed, and a *P* value below 0.05 was considered statistically significant.

Results

Thirty ESRD-HD patients were included in the study; 11(36.6 %) diabetics and 19(63.3 %) non-diabetics, aged (57.67±5.59 years) with HD therapy duration of (5.45±2.9 years), 14 (46.7%) men and 16(53.3%) women, and 20 control subject aged 43.75 ±7.85 years). Compared to controls; patients group shows statistically significant higher BMI, serum urea, creatinine, glucose, HbA1c, TG, LDLc, VLDL, HDLc, Non-HDL, visfatin and ferritin; calculated atherogenic risk ratios [VLDL/HDL, Non-HDL/HDL, cholesterol/HDL, LDL/HDL, TG/HDL, LDL/VLDL]; but statistically no significant difference in relation to blood pressure, height and serum cholesterol [Table 1]. Compared to controls; both DM and non-DM patients have higher BMI, TG, LDL-c, VLDL, urea, creatinine, glucose and HbA1c, visfatin and ferritin. Moreover; there are high lipid ratios (VLDL/HDL; Non-HDL/HDL; cholesterol/HDL; LDL/HDL; TG/HDL and LDL/ VLDL).

Table 1. Comparison between ESRD-HD Cases versus Control.

Variables	Cases (No=30)	Control (No=20)	P value
Age (years)	57.67±5.59	43.75±7.85	**<0.001****
Systolic BP (mmHg)	124.33±15.46	120.0±10.26	0.277
Diastolic BP (mmHg)	80.0±8.30	76.0±5.03	0.060
Weight (kg)	77.83±13.91	68.67±10.74	**0.016***
Height (cm)	170.80±13.85	170.90±10.61	0.978
BMI (kg/m²)	26.23±4.07	23.30±2.51	**0.006***
Cholesterol (mg/dL)	153.93±31.14	149.66±30.41	0.634
HDLc (mg/dL)	27.97±5.70	50.24±4.00	**<0.001****
Non-HDL (mg/dL)	125.97±36.03	99.42±30.17	**0.009***
Triglyceride (mg/dL)	150.40±77.68	73.94±7.47	**<0.001****
LDLc (mg/dL)	85.37±25.28	62.55±5.61	**<0.001****
VLDL (mg/dL)	30.08±15.54	14.81±1.49	**<0.001****
VLDL/HDL	1.17±0.78	0.296±0.036	**<0.001****
Non-HDL/HDL	5.05±2.89	2.0±0.64	**<0.001****
Total cholesterol/HDL	6.09±2.86	2.99±0.64	**<0.001****
LDL/HDL	3.20±1.01	1.26±0.16	**<0.001****
TG/HDL	5.87±3.87	1.48±0.18	**<0.001****
LDL/VLDL	3.39±1.47	4.15±0.78	**0.045***
Urea (mg/dL)	90.62±40.51	43.96±11.30	**<0.001****
Creatinine (mg/dL)	6.31±3.87	0.74±0.42	**<0.001****
Glucose (mg/dL)	118.73±52.58	77.60±6.64	**0.001****
HbA1c %	5.86±1.47	5.00±0.33	**0.014***
Visfatin (µg/L)	15.34±1.73	9.45±1.36	**<0.001****
Ferritin (ng/ml)	1097±598	59.98±34.44	**<0.001****

*Significant **highly significant / BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; TG: triglyceride; HbA1c: glycated hemoglobin

Visfatin level shows no significant difference between DM and non-DM patients. There was insignificant difference between male and female patients and insignificant difference between patients with serum ferritin (200> serum ferritin >800 ng/ml) and (800> serum ferritin> 2000 ng/ml); regarding all parameters of demographic, serum biochemical values and calculated atherogenic ratios (data not shown).

Table 2. Spearman's correlation between visfatin and ferritin with other laboratory finding in ESRD-HD patients.

Variable	Visfatin		Ferritin	
	r	P value	r	P value
Duration of HD	-0.11	0.66	0.304	0.102
Systolic BP (mmHg)	-0.23	0.21	-0.101	0.594
Diastolic BP (mmHg)	0.21	0.27	**-0.559**	**0.001****
Weight (kg)	0.35	0.06	-0.053	0.779
Height (cm)	-0.34	0.06	0.107	0.574
BMI (kg/m²)	**0.82**	**<0.001****	-0.114	0.548
Total Cholesterol (mg/dL)	**0.98**	**<0.001****	-0.159	0.401
HDLc (mg/dL)	**-0.85**	**<0.001****	0.167	0.377
Non-HDL (mg/dL)	**0.98**	**<0.001****	-0.164	0.387
Triglyceride (mg/dL)	0.20	0.28	-0.139	0.464
LDLc (mg/dL)	-0.09	0.62	0.307	0.099
VLDL (mg/dL)	0.20	0.28	-0.139	0.464
VLDL/HDL	**0.49**	**0.006***	-0.234	0.214
Non-HDL/HDL	**0.86**	**<0.001****	-0.189	0.316
Cholesterol/HDL	**0.85**	**<0.001****	-0.212	0.261
LDL/HDL	**0.51**	**0.004***	0.083	0.663
Triglyceride/HDL	**0.47**	**0.009***	-0.239	0.203
LDL/VLDL	-0.29	0.12	0.248	0.186
Urea (mg/dL)	-0.01	0.98	-0.070	0.715
Creatinine (mg/dL)	-0.20	0.29	-0.166	0.380
Glucose (mg/dL)	0.26	0.17	0.072	0.704
HbA1c %	0.23	0.21	0.196	0.299
Ferritin (ng/ml)	-0.19	0.31	-	-
Visfatin (µg /L)	-	-	-0.190	0.314

*Significant **highly significant/ BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; TG: triglyceride; HbA1c: glycated hemoglobin

Correlation between visfatin and ferritin with other clinical and laboratory finding in ESRD-HD: [Table 2].

- **Visfatin;** shows inverse correlation with HDL-c (r=-0.85, P=<0.001) and positive correlation with BMI (r=0.82, P=<0.001), both cholesterol and Non-HDL (r=0.98, P=<0.001), VLDL/HDL (r= 0.49, P=0.006), Non-HDL/HDL (r=0.86, P=<0.001), cholesterol/HDL (r=0.85, P=<0.001), LDL/HDL (r=0.51, P=0.004), TG/ HDL (r=0.47, P=0.009).
- **Ferritin;** shows inverse correlation with diastolic BP (r=-0.559, P=0.001).
- Both visfatin and ferritin shows insignificant correlation with disease duration, systolic blood pressure, s. urea and creatinine.

Multiple linear stepwise regression analysis confirmed that the following three ratios to be significant predictors of CVD risk in ESRD-HD patients (cholesterol/HDL, LDL/HDL and TG/HDL); while VLDL/HDL is not risk factor [Table 3].

Table 3. Logistic Regression (Odd's Ratio) for Cardiac risk factors for heart attack in ESRD-HD patients.

Variable	Odd's ratio (OR)	95% CI		P value
		Lower	Upper	
Cholesterol/HDL	25.07	3.09	203.3	**0.003***
LDL/HDL	3.44	1.31	9.03	**0.043***
Triglyceride/HDL	6.45	1.63	2.55	**0.038***
VLDL/HDL	1.12	124.9	1.09	**0.025***

*Significant/ HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein

Logistic regression analysis reveals that the risk of CHD in ESRD-HD patients is significantly associated with BMI, TG, non-HDL, LDL-C, VLDL, urea, glucose, HbA1c, and ferritin [Table 4].

Table 4. Logistic Regression (Odd's Ratio) for ESRD-HD patients.

Variable	Odd's ratio (OR)	95% CI		P value
		Lower	Upper	
Systolic BP (mmHg)	1.02	0.98	1.1	**0.273**
Diastolic BP (mmHg)	1.08	0.99	1.2	**0.07**
Weight (kg)	1.06	1.0	1.1	**0.02***
Height (cm)	1.0	0.95	1.05	**0.98**
BMI (kg/m²)	**1.3**	1.06	1.6	**0.01***
Total cholesterol (mg/dL)	1.0	0.99	1.02	**0.63**
HDLc (mg/dL)	0.005	0.0	-	**0.99**
Non-HDL (mg/dL)	1.02	1.0	1.04	**0.01***
Triglyceride (mg/dL)	1.1	1.02	1.13	**0.004***
LDLc (mg/dL)	1.2	1.07	1.3	**0.001***
VLDL (mg/dL)	1.4	1.1	1.8	**0.004***
LDL/VLDL	0.59	0.35	1.02	**0.06**
Urea (mg/dL)	1.1	1.04	1.2	**0.002***
Creatinine (mg/dL)	**8.1**	0.0	-	**0.95**
Glucose (mg/dL)	1.2	1.0	1.3	**0.004***
HbA1c %	**2.2**	1.1	4.5	**0.03***
Visfatin (µg /L)	**4.0**	0.0	-	**0.99**
Ferritin (ng/ml)	1.0	1.0	1.1	**0.03***

*Significant/ BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; HbA1c: glycated hemoglobin

Discussion

Many studies recognized a link between CVS disease, inflammation and mortality. Inflammation is a principal component of almost all kidney diseases histological features [23]. Failing renal function may upturn overall inflammatory responses because of the decreased renal clearance of factors involved in inflammation [24]. There is cumulative evidence that hypervisfatinaemia is associated with impaired endothelial function and higher mortality in ESRD patients [25]. Moreover dyslipidemia in CKD was associated with cellular oxidative injury that may contribute to pro-inflammatory and pro-thrombotic milieu [26]. Our results show a high level of visfatin in ESRD-HD patients compared to controls. This is in agreement with [2,25,27-30]. However; Soyoral et al, found that visfatin level does not differ between dialysis patients and healthy individuals [31]. The reason for such observation is not clear, but diminished clearance secondary to low glomerular filtration in renal damage or excessive release from progressively damaging renal cells in advance stages (as visfatin located intra-cellular and releases upon cell lyses) [32]. Our results showed that ESRD-HD patients have an elevated atherogenic lipid profile, with significantly lower serum HDL and significantly higher non-HDL, TG, LDL, VLDL together with calculated risk ratios for VLDL/HDL, non-HDL/HDL, Cholesterol/HDL, LDL/HDL, TG/HDL, LDL/VLDL compared to controls; and this was more intensified in diabetic patient. This is in agreement with Soyoral et al, but with insignificant difference between males and females [31]. Also in agreement with Raju et al, but found that LDL was not altered in HD patients compared to control group [33]. In contrast; Yamamoto et al, found insignificant differences in total cholesterol, triglyceride and HDL levels between patients with ESRD-HD and controls however he recognized abnormal HDL capacity to mediate cholesterol efflux [34]. Our results show insignificant difference between male and female patients regarding age, duration of dialysis, blood pressure, BMI, kidney function tests, lipid profile, glucose, HbA1c, ferritin, visfatin and lipid-related atherogenic risk ratios. In contrast Mitwalli et al, observed that female patients had higher serum levels of triglycerides, HDL, total cholesterol, and LDL while Kim et al, found that atherogenic ratios are highly significant in women [3,35].

Visfatin; showed significant positive correlation with (BMI, cholesterol, non-HDL, VLDL/HDL, non-HDL/HDL, Cholesterol/HDL, LDL/HDL, TG/ HDL) and significant inverse correlation with HDL-c (these factors are the component of metabolic syndrome), this was in agreement with Mu et al, [36]. In contrast; Chen et al, Zahorska-Markiewicz et al, and Soyoral et al, found no correlation between visfatin level and BMI and lipid profile values or atherogenic risk ratios [15,31,37]. Chen et al, did not find any relationship between visfatin and LDL-c, total cholesterol, or triglyceride levels in obese individuals. While Smith et al, found that visfatin was positively correlated with HDL-c and negatively correlated with LDL-c, and Wang et al, in a study involving 35 subjects with hyperlipidemia and insulin resistance, reported that visfatin was positively correlated with HDL-c and negatively correlated with triglycerides [38-40]. Linear stepwise regression analysis results revealed that visfatin levels may be affected by HDL-c levels, and logistic regression analysis showed that visfatin was an independent risk factor of CVD. This result indicates that visfatin could be involved in lipid metabolism, which leads to the occurrence of CVD. Our results showed high serum ferritin level in ESRD-HD patients and this was more intensified in diabetic patient; with insignificant difference between male and female cases. This was in agreement with Kalantar-Zadeh et al, and Soyoral et al, [31,41]. Plasma ferritin level represents the balance between its secretion, which is directly related to intracellular iron synthesis, and its clearance [41]. In dialysis patients, hyperferritinaemia is associated with erythropoietin resistance and more severe anemia and according to K/DOQI guidelines iron administration should be suspended if serum ferritin is >800 ng/ml, meanwhile iron overload with its poor clinical outcome may follow [19,42]. In a population-based prospective cohort and cross-sectional study both point out high serum ferritin to be associated with type 2 DM prevalence [43,44]. However; high ferritin level found to be associated with insulin resistance in type 2 DM and metabolic syndrome in men and in women [45-47]. On performing regression analyses, total cholesterol/HDL ratio gives maximum among the four ratios; approximately (25%) to the risk of developing CVD while TG/HDL ratio (6%) and LDL/HDL ratio (3%) whereas VLDL/HDL ratio is not a risk factor. This was in line with [48-51]. In addition; serum visfatin, creatinine and HbA1C were found to be risk factors for CVD, while ferritin and HDL-c were not a risk factor.

Limitation

All of our DM patients were on ACE inhibitor, which has shown to recover endothelial function; therefore their use may lead to some confusing effect. Furthermore; the cross-sectional study design that cannot understand causality.

Conclusion

dyslipidemia, hyper-visfatinaemia and hyper-ferritinemia established in ESRD patient's all of which are independent risk factors for CVD; using atherogenic risk ratios as screening tool for CVD risk estimation is useful particularly in centers with deficient incomes.

Recommendations

lifestyle changes, inflammation management and lipid regulation are essential to improve outcome in ESRD patients.

Conflict of Interest

I declare that we have no conflict of interest.

Acknowledgements

We would like to thank staff members of nephrology unit at Luxor general hospital, Luxor- Egypt.

References

1 Zeidan AM, Sharara MG, Suliman SH, Zeid MM, Zytoun SS, Nomeir MH: Novel Markers for Endothelial Dysfunction in Chronic Kidney Disease. Life Sci J. 2012; 9(2):23-35.

2 Yilmaz IM, Saglam M, Carrero JJ, Quresh RA, Caglar K, Eyileten T, et al. Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. Nephrol Dial Transplant. 2008; 23(3): 959-965.

3 Kim JY, Kang HT, Lee HR, Lee YJ, Shim JY: Comparison of Lipid-Related Ratios for Prediction of Chronic Kidney Disease Stage 3 or More in Korean Adults. J Korean Med Sci. 2012; 27: 1524-1529.

4 Rabe K, Lehrke M, Parhofer KG, Broedl UC. Adipokines and insulin resistance. Mol Med. 2008; 14: 741–51.

5 Adeghate E: Visfatin: Structure, Function and Relation to Diabetes Mellitus and Other Dysfunctions. Curr Med Chem. 2008; 15(18):1851-1862.

6 Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, et al. Visfatin, an adipocytokine with pro-inflammatory and immune-

modulating properties. J Immunol. 2007; 178(3):1748-58.
7 Malyszko J, Malyszko JS, Mysliwiec M. Visfatin and endothelial function in dialyzed patients. Nephrology (Carlton). 2010; 15: 190–196.
8 Vanhoutte PM. Endothelial dysfunction: the first step toward coronary arteriosclerosis. Circ J. 2009; 73:595e601.
9 Luk T, Malam Z, Marshall JC. Pre-B cell colony-enhancing factor (PBEF)/visfatin: visfatin novel mediator of innate immunity. J Leukoc Biol. 2008; 83:804-16.
10 Andrews NC. Anemia of inflammation: the cytokine-hepcidin link. J Clin Invest. 2004; 113:1251–1253.
11 Thomas CE, Morehouse LA, Aust SD. Ferritin and superoxide-dependent lipid peroxidation. J Biol Chem. 1985; 260:3275-3280
12 Bertelsen M, Ánggard EE, Carrier MJ. Oxidative stress impairs insulin internalization in endothelial cells in vitro. Diabetologia. 2001; 44:605- 613.
13 Fernández-Real JM, Lo´ pez-Bermejo A, Ricart-Engel W: Cross-talk between iron metabolism and diabetes. Diabetes. 2002; 51: 2348-2354.
14 Iwasaki T, Nakajima A, Yoneda M, Yamada Y, Mukasa K, Fujita K, et al. Serum ferritin is associated with visceral fat area and subcutaneous fat area. Diabetes Care. 2005; 28: 2486–2491.
15 Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ, et al. Elevated plasma level of visfatin/ pre-B cell colony enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2006; 91: 295-9.
16 Fernández-Real JM, Moreno JM, Chico B, López-Bermejo A, Ricart W. Circulating visfatin is associated with parameters of iron metabolism in subjects with altered glucose tolerance. Diabetes Care. 2007; 30(3): 616-21.
17 Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999; 340:448-454.
18 Rifkin DE, Sarnak MJ. Does inflammation fuel the fire in CKD? Am J Kidney Dis. 2009; 53:572-575 .
19 Gunnell J, Yeun JY, Depner TA, Kaysen GA. Acute-phase response predicts erythropoietin resistance in hemodi¬alysis and peritoneal dialysis patients. Am J Kidney Dis. 1999; 33:63-72.
20 Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. Nephrol Dial Transplant. 2004; 19:141-149.
21 Hasuike Y, Nonoguchi H, Tokuyama M, Ohue M, Nagai T, Yahiro M, et al. Serum ferritin predicts prognosis in hemodialysis patients: the Nishinomiya study. Clin Exp Nephrol. 2010; 14:349-355.
22 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972, 18: 499-502.
23 Fogo AB. Mechanisms of progression of chronic kidney disease. Pediatr Nephrol. 2007; 22: 2011-2022.
24 Malyszko J, Malyszko JS, Pawlak K, Mysliwiec M. Visfatin and apelin, new adipocytokines, and their relation to endothelial function in patients with chronic renal failure. Adv in Med Sci. 2008; 53(1): 32-36.
25 Nüsken K, Petrasch M, Rauh M, Stohr W, Nusken E, Schneider H, et al. Active visfatin is elevated in serum of maintenance hemodialysis patients and correlates inversely with circulating HDL cholesterol. Nephrol Dial Transplant. 2009; 24: 2832-2838.
26 Keane WF, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease: implications for the pathophysiology of atherosclerosis. J Atheroscler Thromb. 2013; 20(2):123-33.
27 Axelsson J, Witasp A, Carrero JJ, Qureshi AR, Suliman ME, Heimbürger O, et al. Circulating levels of visfatin/pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. Am J Kidney Dis. 2007, 49(2): 237-244.
28 Erten Y, Ebinc FA, Ebinc H, Pasaoglu H, Demirtas C, Tacoy G, et al. The relationship of visfatin levels to inflammatory cytokines and left ventricular hypertrophy in hemodialysis and continuous ambulatory peritoneal dialysis patients. Ren Fail. 2008, 30:617-623
29 Yilmaz MI, Saglam M, Qureshi AR, Carrero JJ, Caglar K, Eyileten T, et al. Endothelial dysfunction in type-2 diabetics with early diabetic nephropathy is associated with low circulating adiponectin. Nephrol Dial Transplant. 2008b; 23:1621-7.
30 Mahmood Nosheen, Abdul Manan Junejo, Jamal Qamar, Awan Rashid. Association of visfatin with chronic kidney disease in a cohort of patients with and without diabetes. J Pak Med Assoc. 2010; 60(11): 922-926.
31 Soyoral YU, Erkoc R, Begenik H, Aldemir MN, Kucukoglu ME. Relationship between visfatin and some clinical and biochemical parameters in peritoneal dialysis patients. J Pak Med Assoc. 2012; 62(11):1179-83.
32 Kitani T, Okuno S, Fujisawa H. Growth phase-dependent changes in the subcellular localization of pre-B-cell colony-enhancing factor. FEBS Lett. 2003; 544: 74–78.
33 Raju DSSK, Lalitha DL, Kiranmayi P. A Study of Lipid Profile and Lipid Peroxidation in Chronic Kidney Disease with Special Reference to Hemodialysis. J Clinic Res Bioeth. 2013; 4: 143.
34 Yamamoto S, Yancey PG, Ikizler TA, Jerome WG, Kaseda R, Cox B, et al. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. J Am Coll Cardiol. 2012; 60(23):2372-9.
35 Mitwalli A H, Alam AA, Al Wakeel J S., Isnani AC. Dyslipidemia in Dialysis Patients. Saudi J Kidney Dis Transpl. 2011; 22(4):689-694.

36 Mu J, Feng B, Ye Z, Yuan F, Zeng W, Luo Z, et al. Visfatin is related to lipid dysregulation, endothelial dysfunction and atherosclerosis in patients with chronic kidney disease. J Nephrol. 2011; 24(2): 177-184.

37 Zahorska-Markiewicz B, Olszanecka-Glinianowicz M, Janowska J, Kocelak P, Semik-Grabarczyk E, Holecki M, et al. Serum concentration of visfatin in obese women. Metabolism. 2007; 8: 1131-4.

38 Chen CC, Li TC, Li CI, Liu CS, Lin WY, Wu MT, et al. The relationship between visfatin levels and anthropometric and metabolic parameters: association with cholesterol levels in women. Metabolism. 2007; 56: 1216-20.

39 Smith J, Al-Amri M, Sniderman A, Cianflone K. Visfatin concentration in Asian Indians is correlated with high density lipoprotein cholesterol and apolipoprotein A1. Clin Endocrinol. 2006; 65: 667-72.

40 Wang P, van Greevenbroek MM, Bouwman FG, Brouwers MC, van der Kallen CJ, Smit E, et al. The circulating PBEF/ NAMPT/visfatin level is associated with a beneficial blood lipid profile. Pflugers Arch. 2007; 454: 971-6.

41 Kalantar-Zadeh K, Don BR, Rodriguez RA, , Humphreys MH. Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. Am J Kidney Dis. 2001; 37: 564-572.

42 National Kidney Foundation I, Kidney-Dialysis Outcome Quality Initiative. K/DOQI clinical practice guidelines: anemia. Am J Kidney Dis. 2001; 37 [Suppl 1].

43 Montonen J, Boeing H, Steffen A, Lehmann R, Fritsche A, Joost HG, et al. Body iron stores and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. Diabetologia. 2012; 55(10): 2613-21.

44 Yeap BB, Divitini ML, Gunton JE, , Olynyk JK, Beilby JP, McQuillan B, et al. Higher ferritin levels, but not serum iron or transferrin saturation, are associated with Type 2 diabetes mellitus in adult men and women free of genetic haemochromatosis. Clin Endocrinol (Oxf). 2015; 82(4):525-32.

45 Kim CH, Kim HK, Bae SJ, Park JY, Lee KU. Association of elevated serum ferritin concentration with insulin resistance and impaired glucose metabolism in Korean men and women. Metabolism. 2011; 60(3):414-20.

46 Pham NM, Nanri A, Yi S, Kurotani K, Akter S, Foo LH, et al. Serum ferritin is associated with markers of insulin resistance in Japanese men but not in women. Metabolism. 2013; 62(4):561-7.

47 Yu FJ, Huang MC, Chang WT, Chung HF, Wu CY, Shin SJ, et al. Increased ferritin concentrations correlate with insulin resistance in female type 2 diabetic patients. Ann Nutr Metab. 2012; 61(1):32-40.

48 Genest J, Frohlich J, Fodor G, McPherson R. The Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. CMAJ. 2003; 169:921-924.

49 Subia J, Afshan S. Comparison of CVD risk associated with the long term use of contraceptives in young females. J App Pharm Sci. 2012; 2(11): 062-066.

50 Bhardwaj S, Bhattacharjee J, Bhatnagar MK, Tyagi S. Atherogenic index of plasma, castelli risk index and atherogenic coefficient- new parameters in assessing cardiovascular risk. Int J Pharm Bio Sci. 2013; 3:359-64.

51 Nimmanapalli HD, Kasi AD, Devapatla Pk, Nuttakki V. Lipid ratios, atherogenic coefficient and atherogenic index of plasma as parameters in assessing cardiovascular risk in type 2 diabetes mellitus. Int J Res Med Sci. 2016; 4(7): 2863-2869.