Journal of Diabetes and Its Complications 33 (2019) 107422

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Clinical Research

Resistin as a predictor of cardiovascular hospital admissions and renal deterioration in diabetic patients with chronic kidney disease

Bruno Bonito [a,*,1], Ana Paula Silva [a,b,1], Fátima Rato [c], Nélio Santos [c], Pedro Leão Neves [a,b]

[a] Nephrology Department, Centro Hospitalar Universitário do Algarve, Faro, Portugal
[b] Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
[c] Clinical Pathology, Centro Hospitalar Universitário do Algarve, Faro, Portugal

ARTICLE INFO

Article history:
Received 7 May 2019
Received in revised form 31 July 2019
Accepted 17 August 2019

Keywords:
Type 2 diabetes
Resistin
CVD
CKD
ESRD

ABSTRACT

Background: High resistin levels have been associated with cardiovascular disease (CVD). Cardiovascular hospitalizations are common, especially in diabetic and renal impaired patients. The purpose of this study is to determine the role of serum resistin as a predictor of cardiovascular hospitalizations in type 2 diabetic patients with mild to moderate chronic kidney disease (CKD).

Methods: We conducted a prospective, observational study. 78 diabetic patients with mild to moderate CKD and no previous CVD were included. The population was divided in two groups: G-1 with cardiovascular related admission (n = 13) and G-2 without cardiovascular related admission (n = 65). A Student's *t*-test was conducted to determine correlations between laboratory findings and hospitalization. We used logistic regression to assess predictors of cardiovascular events requiring hospitalization and Cox regression to identify predictors of end-stage renal disease (ESRD).

Results: eGFR, albumin, HbA1c, phosphorous, PTH, IR, CRP, resistin and active vitamin D, were related to cardiovascular admissions. In a multivariate regression model, resistin (OR = 2.074, $p = 0.047$) was an independent predictor of cardiovascular hospitalization. Cox regression showed that resistin (HR = 1.931, $p = 0.031$) and UACr (HR = 1.151, $p = 0.048$) were also independent predictors of renal disease progression.

Conclusion: Resistin demonstrated to be valuable in predicting hospital admissions and progression to ESRD.

1. Introduction

In humans, resistin gene is located in chromosome 19 with resistin holding a crucial part during inflammation where macrophages are the main responsible for its secretion.[1–3] Due to its resemblance to the traits of a cytokine and its production being associated with immune system cells, resistin has been considered as a possible inflammatory marker in humans.[4–6]

The kidney is where the elimination of resistin occurs, consequently resistin tends to remain in higher concentrations in patients with CKD.[7] Patients on hemodialysis with residual renal function have lower resistin levels, whereas patients on hemodialysis with no residual renal function have higher resistin levels, supporting the hypothesis that resistin is removed by the kidney. Moreover, in patients with CKD, it has been demonstrated that resistin levels and renal function are strongly related.[8] Several studies suggest that resistin serum concentrations may be increased in CKD.[6,9,10] Also, high serum resistin levels have been associated with low glomerular filtration rate (GFR).[11] The excess of cytokines observed in the context of reduced renal function may be related to diminished clearance and renal degeneration through inflammatory pathways that can lead to death.[8] Nevertheless, the exact receptors for resistin are still unknown.[8] Alongside its importance in inflammation, recent investigations suggest that resistin plays a relevant role on several pathological pathways in complex disorders such as diabetes, CVD, liver disease, CKD and auto-immune disease.[1,12]

Chronic cardiovascular damage induces a state of stress which can result in cardiac hypertrophy.[5] The condition is outlined by enlarged cardiomyocytes, raised protein synthesis, elevated brain natriuretic peptide (BNP), atypical sarcomeric organization, as well as enhanced fibronectin production.[5] A recent case-control study suggested that serum resistin level was higher in patients with cardiac failure. Moreover, the levels increased according to the patient's New York Heart Association (NYHA) functional class.[13]

In this study our main objective is to investigate the possible role of resistin as a predictor of hospital admissions caused by cardiovascular disease in a population of type 2 diabetic patients with mild to moderate CKD. We also aim to determine the role of resistin in predicting CKD progression to ESRD.

Conflict of interest statement: None.

* Corresponding author.
E-mail address: brunofbonito@gmail.com (B. Bonito).

[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.jdiacomp.2019.107422
1056-8727/

2. Subjects, materials and methods

This is a prospective, observational study in diabetic patients with mild to moderate CKD. Patients were screened and recruited in an outpatient diabetic nephropathy clinic and were followed from January 2010 to December 2018.

In this study 78 patients with type 2 diabetes and mild to moderate CKD (15 mL/min/1.73 m^2 < eGFR ≤ 89 mL/min/1.73 m^2) were included. The classification of diabetes followed the guidelines established by the American Diabetes Association.[14] All included patients were, at the time of inclusion, undergoing several pharmacologic therapies, namely: antihypertensive drugs such as angiotensin receptor antagonists (ARA), angiotensin converting enzyme inhibitors (ACE-I) and calcium channel blockers (CCB) anti-dyslipidemia drugs, acetylsalicylic acid (ASA), and oral antidiabetic agents.

Patients' follow up was conducted two to three times a year during in-person appointments at the nephrology clinic. Patients with more severe conditions returned approximately every 3 months, while others returned every 6 months. No patient was "lost to follow up".

2.1. Exclusion criteria

Patients were considered ineligible to participate in the study if they presented at least one of the following criteria: previous CVD (defined as a history of one or more of the following: non-fatal myocardial infarction, stable or unstable angina pectoris, stroke or transient ischemic attacks and heart failure), history of valvopathies (including rheumatic fever), uncontrolled hypertension under antihypertensive therapy, estimated glomerular filtration rate (eGFR) ≤ 15 mL/min or ≥90 mL/min, type 1 diabetes, renal disease other than diabetic nephropathy, and neoplastic or infectious diseases. Patients were not allowed to undergo therapy with thiazide and loop diuretics simultaneously, spironolactone, magnesium supplements, or any laxative or chelate agent containing magnesium. Patients with any gastrointestinal pathology that could possibly interfere with magnesium absorption were also not included in this study.

2.2. Data collection, analysis and ethical considerations

The evaluation and characterization of the hospitalization were based on the admission clinical record, which provides information regarding signs and symptoms, diagnostic exams, procedures, treatments, and diagnosis on the day of discharge.

Serum samples were collected at baseline in fasting patients. Samples were centrifuged, and plasma was frozen at −80 °C. Several laboratory parameters were analyzed: HbA1c, total cholesterol, mineral metabolism (phosphorus, PTH), inflammation (CRP), active form of vitamin D [1,25(OH)2D3] and serum creatinine.

Total cholesterol and phosphorus were measured using the ARCHITECT c Systems and the AEROSET System (Abbott Diagnostics Division, Abbott Laboratories Abbott Park, Illinois, USA). HbA1c and PTH levels were measured using a spectrophotometry technique and electrochemiluminescent immunoassays (ECLIA), respectively.

Plasma resistin levels were determined by enzyme-linked immunosorbent assay using the "Resistin (Human)" ELISA kit (Cat. No. EK-028-36, Phoenix Pharmaceuticals Inc., Burlingame, California, USA), according to manufacturer's instructions, adapted to the Triturus automatic microplate apparatus (Grifols S.A., Barcelona, Spain). Results were calculated using the apparatus curve-fitting software in 4 parameter logistics mode.

Values of serum creatinine were obtained through an enzymatic method, using the ARCHITECT device (Abbott Diagnostics Division, Abbott Laboratories Abbott Park, Illinois, USA). We estimated the glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15]

2.3. Definitions

Cardiovascular events with hospitalization were classified upon discharge, considering only admissions caused by coronary heart disease (myocardial infarction, stable or unstable angina pectoris), congestive heart failure, peripheral vascular disease and cerebrovascular disease (stroke or transient ischemic attacks) based on recent international guidelines.[16]

According to the presence or absence of cardiovascular hospital admission during the study period, our population was divided into two groups: G-1, with cardiovascular hospitalization (n = 13), and G-2, without cardiovascular hospitalization (n = 65).

2.4. Statistical analysis

The data were inserted and arranged using a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet. Statistical analysis was performed using the program Statistical Package for the Social Sciences (SPSS) (version 24, IBM Corporation, Armonk, NY, USA). Quantitative results were expressed as mean ± standard deviation (SD) for continuous variables with normal distribution, in accordance with the Kolmogorov-Smirnov distribution test. Differences between groups were assessed using independent samples *t*-test and Fisher's exact test for continuous and categorical variables.

The independent variables associated with cardiovascular hospitalization were identified by regression models. Variables included in these models were: gender, age, eGFR, albumin, HbA1C, phosphorus, PTH, urine albumin/creatinine ratio (UACr), insulin resistance, CRP, resistin, and systolic blood pressure (BP). The independent variables associated with progression to ESRD were assessed by Cox regression model. The statistical tests ran with data from 77 patients due to a missing HbA1C value in one of our patients. However, in descriptive statistics we included data regarding the patient with no HbA1C value.

A *p*-value inferior to 0.05 was considered as representing statistical significance.

Before its implementation, the study was approved by the local Ethics Committee. All principles of the Declaration of Helsinki of 1975, as revised in 2000, were followed and study procedures were only conducted after obtaining patients' written informed consent. The anonymity and confidentiality of the patients was guaranteed throughout the entire study.

3. Results

For a better sample characterization, a set of important demographic and clinical data were included as seen in Table 1. This sample consisted of a total of 78 patients (n = 78), age ranged from 32 to 87 years old and the mean age was 61 years and resistin ranged from 1.56 ng/mL to

Table 1
Summary demographics of our cohort.

	n	Minimum	Maximum	Mean	Std. deviation
eGFR (mL/min/1.73 m^2)	78	16.20	87	42.9	21.4
Albumin (g/dL)	78	1.50	5.60	4.15	0.60
Total cholesterol (g/dL)	78	74	318	192.95	39.96
Hb (g/dL)	78	7.50	16.80	12.66	1.92
HbA1c (%)[a]	77	5.20	13.10	7.50	1.45
Phosphorous (mg/dL)	78	2.30	9.40	4.32	1.20
PTH (pg/ml)	78	13.00	675.00	136.31	16.18
Urinary albumin/creatinine ratio (UACr) (μg/mg)	78	36.00	550.00	245.10	27.04
HOMA-IR	78	0.34	5.75	2.13	1.75
CRP (mg/L)	78	0.01	5.80	1.60	1.34
Resistin (ng/mL)	78	1.56	11.80	5.98	3.50
Active vitamin D (ng/mL)	78	7.40	34.00	19.45	8.10

[a] There was one missing value for HbA1c.

Table 2
Differences between groups (G-1 with cardiovascular hospital admission and G-2 without cardiovascular hospital admission).

	G-1 (n = 13)		G-2 (n = 65)		p
Gender (f/m)	4/9		26/39		0.384
BMI (kg/m^2)	24.16	±2.67	24.07	±3.26	0.289
eGFR	22.64	±10.11	44.51	±24.30	<0.001
Albumin	3.70	±0.82	4.24	±0.51	0.003
Total cholesterol (g/dL)	178.15	±41.63	195.91	±39.23	0.145
Hb	12.25	±1.60	12.75	±1.98	0.395
HbA1c[a]	6.55	±0.68	7.69	±1.49	<0.001
Phosphorous	5.25	±1.44	4.13	±1.07	0.002
PTH	243.92	±146.71	114.78	±81.89	<0.001
UACr	249.54	±110.74	244.21	±119.07	0.882
HOMA-IR	3.54	±0.86	1.86	±1.75	<0.001
CRP	2.69	±0.48	1.39	±1.36	<0.001
Resistin	9.08	±1.56	5.35	±3.45	<0.001
Active vitamin D	9.32	±1.46	21.48	±7.32	<0.001
Renin-angiotensin system inhibitor (%)	78.7		80.7		0.184
Renoprotective CCB (%)	35.6		48.6		0.151

[a] For HbA1c G-1 had n = 13 and G-2 n = 64, due to a missing value.

11.80 ng/mL with a mean of 5.98 ng/ml. Out of the 78 patients, 13 had hospital admissions related to newly diagnosed cardiovascular events.

Subjects were classified into two groups according to cardiovascular hospital admission during the study period: G-1 with cardiovascular related hospital admission (n = 13) and G-2 without cardiovascular related hospital admission (n = 65).

A Student's t-test was conducted to compare the mean values of each variable with and without hospital admission due to cardiovascular events. Table 2 illustrates the differences between the two groups. G-1 patients had higher Phosphorous ($p = 0.002$), PTH ($p < 0.001$), insulin resistance ($p < 0.001$), CRP ($p < 0.001$), resistin ($p < 0.001$) and lower eGFR ($p < 0.001$), albumin ($p < 0.003$), HbA1C ($p < 0.001$) and active vitamin D ($p < 0.001$). There was no difference between groups in gender, BMI, cholesterol, Hemoglobin (Hb), UACr or in antihypertensive therapy.

A multivariate logistic regression model showed that resistin (OR = 2.074, 95% CI (1.557–7.729) $p = 0.047$) was an independent predictor of cardiovascular hospital admissions in diabetic patients with mild to moderate CKD (Table 3).

From our total population, 19 patients progressed to ESRD, requiring renal function replacement techniques such as hemodialysis or peritoneal dialysis. We used Cox regression to investigate predictors of renal deterioration and resistin (HR = 1.931, $p = 0.031$) and UACr (HR = 1.151, $p = 0.048$) was an independent predictor of renal disease progression when adjusted to other variables (Table 4).

4. Discussion

Our findings suggest that resistin levels can predict cardiovascular related hospital admissions in type 2 diabetic patients with CKD.

Table 3
Logistic regression: predictors of cardiovascular event related hospital admission.

	OR	95% CI	p
Gender	1.308	0.367–3.004	0.460
Age	1.002	0.900–1.500	0.152
eGFR	0.450	0.708–2.405	0.125
Albumin	0.678	0.305–1.300	0.200
HbA1C	0.473	0.126–1.004	0.084
Phosphorous	1.334	0.563–4.084	0.075
PTH	1.019	0.993–1.046	0.148
UACr	1.001	0.989–1.013	0.915
Insulin resistance	0.082	0.004–1.632	0.101
CRP	3.238	0.400–6.224	0.271
Resistin	2.074	1.557–7.729	0.047
Systolic BP	1.026	0.923–1.139	0.638

Table 4
Predictors of renal disease progression.

	HR	95% CI	p
eGFR	0.961	0.929–1.994	0.222
Age	0.994	0.955–1.035	0.765
Gender	1.389	0.478–4.036	0.546
BMI	0.946	0.813–1.100	0.470
Phosphorous	1.187	0.734–1.921	0.485
UACr	1.151	1.097–2.004	0.048
HgA1c	0.875	0.509–1.503	0.875
Albumin	0.909	0.302–2.732	0.909
Insulin resistance HOMA	1.156	0.573–2.334	0.686
CRP	0.854	0.391–1.863	0.691
Resistin	1.931	1.014–3.310	0.031
Active vitamin D	0.973	0.872–1.084	0.616
Cardiovascular hospital admission			
G-2	Ref	Ref	R
G1	0.978	0.570–3.450	0.058

Resistin and UACr were independent predictors of progression to ESRD. In addition, we observed a relation between unregulated mineral metabolism, poor glycemic control, deteriorated renal function and inflammation with cardiovascular events requiring hospitalization.

Diabetes mellitus (DM) and CKD represent a major global health concern. DM is the single most important risk factor for renal disease with predictions pointing at a total of 10% of adults suffering from diabetes in the next ten years.[17,18] When compared to the nondiabetic population, these patients are more susceptible to severe renal disease and cardiovascular morbidity.[17,19] A study by Menzaghi et al. proved that patients with type 2 DM have a higher risk of developing CVD when compared to the nondiabetic population, underlining cardiovascular complications as the main cause of death amongst these patients.[20]

Preceding studies have linked resistin with obesity and the etiology of DM.[21,22] Additionally, inadequate glycemic control in diabetic patients has been linked to cardiovascular deterioration.[23–25] One particular study concluded that patients with increased HbA1c variation had higher risk of cardiovascular incidents, but only for eGFR above 60 min/mL/1.73 m^2. They did not demonstrate any relation in patients with eGFR lower than 60 min/mL/1.73 m^2. Our results underline poor glycemic control as a risk factor for cardiovascular events. Insulin resistance (IR) represents an inadequate response to insulin and has been observed not only in diabetic patients, but also in the nondiabetic population with CKD.[26] Although previous studies had conflicting results regarding IR and its role in cardiovascular disease,[18] other studies involving diabetic and nondiabetic populations suggested that IR is an independent risk factor for CVD,[27–29] which is concordant to our findings that homeostatic model assessment insulin resistance (HOMA-IR) is a risk factor for cardiovascular deterioration in diabetic patients.

The importance of mineral metabolism for heart disease is well established.[30] It has been previously observed that vitamin D plays an important cardioprotective role.[31–33] Even though, two large studies failed to conclude that vitamin D improves heart function,[34,35] further research on these studies and their cohort, revealed better outcomes with less cardiovascular hospital admissions in the groups taking vitamin D. More recently, it has been verified that administering vitamin D to diabetic model rats reduced heart volume and fibrosis, which strengthens the previous hypothesis that vitamin D decreases cardiovascular remodeling.[36] Phosphorous has been associated with left ventricular hypertrophy (LVH), but the literature lacks studies without confounding factors.[36] Nevertheless, a recent study demonstrated that phosphorous was not only individually implicated in ventricular hypertrophy, but also in cardiovascular hospital admissions in patients with CKD.[37] PTH has also been associated to LVH in recent studies, however the results are also susceptible to confounding factors.[38,39] In our study we identified mineral metabolism deficiencies as a risk factor for cardiovascular event hospitalization, which is in agreement with what is suggested in recent literature. However, more investigation is

required to exclude confounding factors, such as fibroblast growth factor 23 (FGF-23).

It is known that several traditional risk factors are associated with CKD and CVD. However they have not been able to completely explain the morbidity and mortality in CKD.[18] A study by Stuveling et al. focused on a group of biochemical risk markers in renal patients and found relations with cardiovascular disease, renal deterioration and mortality. In another study of a population of type 2 diabetic patients, it has been proposed that serum resistin levels are higher in patients with lower GFR, and that increasing resistin levels contribute to a decrease in GFR.[40]

As far as we know, although previous investigations aimed to study the role of resistin as a predictor of CVD, our study was the first to relate resistin and CVD in type 2 diabetic patients with mild to moderate CKD. In previous studies of type 2 diabetic populations there was no relation between serum resistin and cardiovascular events.[41,42] Nevertheless, several other studies have linked higher resistin levels with cardiac complications. It was observed that resistin levels are raised in patients with heart failure, and higher levels are associated with higher classes in the NYHA classification.[43,44] Furthermore, a previous study focusing patients on hemodialysis concluded that the effects of resistin in CVD and mortality were evident when the levels of adiponectin (ADPN) were low.[45] Also, multiple studies in different populations and under different conditions, have demonstrated that resistin can predict cardiovascular events.[7,20,45–48]

It has also been suggested, in studies involving resistin, an association between heart failure and its progression with high serum resistin.[49] It has been shown that patients with repetitive coronary events after an acute coronary syndrome had higher serum resistin levels.[50] Moreover, resistin levels predict adverse cardiovascular events in patients with coronary artery disease, including those who were submitted to coronary artery stenting.[51]

In addition, a recent study demonstrated a relation between resistin levels and hospitalization for heart failure in patients already diagnosed with coronary heart disease,[52] which is in line with our findings.

A previous study on a Japanese population demonstrated that serum resistin levels were important for the progression of CKD after adjusting for confounding factors and the mean values of resistin were higher even in early stages of CKD.[53] Our findings after following-up on our population demonstrated that resistin could predict further renal deterioration eventually leading to ESRD. These findings suggest that resistin may have an important part perpetuating renal damage over time in CKD, probably by maintaining an inflammatory environment, which contributes for the progression of the disease. Another study in a hypertensive population concluded that resistin not only was a risk factor for CKD, but also contributed to a poor evolution of the disease by inducing continuous renal damage.[54]

Regardless, our study has limitations. The size of our sample, though large enough to obtain statistically significant results, especially after being divided in G-1 and G2, may not have been sufficiently strong when data were submitted to statistical analysis.

Also, resistin was only measured once and even with strict inclusion/exclusion criteria, we could not account for all confounding factors at the time of measurement. Also, the time between resistin measurement and cardiovascular hospitalization was not considered in our study. Including the time variable in addition to multiple resistin measurements over time would probably provide extra valuable information.

In conclusion, in our type 2 diabetic population with mild to moderate CKD, resistin levels can predict hospitalization due to cardiovascular events. Resistin was also able to predict deterioration of CKD patients into ESRD with the necessity of renal function replacement. However, further research is required in order to understand the mechanism behind these findings and if resistin effects are only a reflection of its activity during inflammatory conditions and reduced GFR. Studies with larger cohorts may be necessary to better understand the role of resistin in diabetic and CKD patients and if it can be a viable tool for clinicians in daily practice to predict cardiovascular disease.

References

1. Jamaluddin MS, Weakley SM, Yao Q, Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. Br J Pharmacol 2012;165:622-32.
2. Repository ZO. University of Zurich. The role of resistin as a regulator of inflammation: implications for various human pathologies. 2009;133:157-70.
3. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. 2001;307–12.
4. Burnett MS, Devaney JM, Adenika RJ, Lindsay R, Howard BV. Cross-sectional associations of resistin, coronary heart disease, and insulin resistance. J Clin Endocrinol Metab 2006;91:64-8.
5. Luo J, Zheng X, Cheng G, Ye Q, Deng Y, Wu L. Resistin-induced cardiomyocyte hypertrophy is inhibited by apelin through the inactivation of extracellular signal-regulated kinase signaling pathway in H9c2 embryonic rat cardiomyocytes. Biomed Reports 2016;2:473-8.Internet. Available from, http://www.spandidos-publications.com/10.3892/br.2016.749.
6. Axelsson J, Bergsten A, Qureshi AR, Heimbürger O, Bárány P, Lönnqvist F, et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. Kidney Int 2006;69:596-604.
7. Chung W, Jung ES, Jung JY, Chang JH, Lee HH, Kim DK, et al. Low resistin level is associated with poor hospitalization-free survival in hemodialysis patients. 2012;377–81.
8. Nagy K, Nagaraju SP, Rhee CM, Mathe Z, Molnar MZ. Adipocytokines in renal transplant recipients. Clin Kidney J [Internet] 2016;9:359-73.Available from:, http://www.ncbi.nlm.nih.gov/pubmed/27274819%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4886901.
9. Dan S, Aditya P, Banerjee P, Bal C, Roy H, Banerjee I. Effect of chronic kidney disease on serum resistin level. 2014;17(6):735–8.
10. Mills KT, Hamm LL, Alper AB, Miller C, Hudaihed A, Balamuthusamy S, et al. Circulating adipocytokines and chronic kidney disease. 2013;8(10):1–5.
11. Akagun T, Caliskan Y, Yazici H, Ozkok A, Telci A, Turkmen A, et al. Elevated resistin levels are associated with inflammation in hemodialysis patients with failed renal allografts. Int J Artif Organs 2014;37:358-63.[Internet]. Available from:, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftp&NEWS=N&AN=00080248-201406150-00002.
12. Mostafazadeh M, Haiaty S, Rastqar A, Keshvari M, Cardiovascular I, Laboratories C, et al. Correlation between resistin level and metabolic syndrome component: a review. Resistin Receptors Resistin and its Secretion 2018;50:521-36.
13. Sciences B. Human resistin in cardiovascular disease 2012;48:27-35.
14. Of S. Carediabetes M Standards of medical care in diabetes — 2017 2017;40:2017.
15. Levey AS, Stevens LA, Frcp C, Schmid CH, Zhang YL, Iii AFC, et al. NIH Public. Access 2009;150:604-12.
16. Investigation O. Comparison of application of the ACC/AHA Guidelines. Adult Treatment Panel III Guidelines, and European Society of Cardiology Guidelines for cardiovascular disease prevention in a European cohort 2015;311:1416-23.
17. Winocour PH. Review article Diabetes and chronic kidney disease: an increasingly common multi-morbid disease in need of a paradigm shift in care. 2017;300–5.
18. Fragoso A, Mendes F, Paula A, Leão P. Insulin resistance as a predictor of cardiovascular morbidity and end-stage renal disease. J Diabetes Complications 2015 https://doi.org/10.1016/j.jdiacomp.2015.05.010. [Internet].
19. Shen Y, Cai R, Sun J, Dong X, Huang R. Diabetes mellitus as a risk factor for incident chronic kidney disease and end-stage renal disease in women compared with men: a systematic review and meta-analysis. Endocrine 2016;87:0-1 https://doi.org/10.1007/s12020-016-1014-6. [Internet].
20. Menzaghi C, Bacci S, Salvemini L, Mendonca C, Palladino G, Fontana A, et al. Serum resistin, cardiovascular disease and all-cause mortality in patients with type 2 diabetes. PLoS One 2013;8:1-9.
21. Matsuda M, Kawasaki F, Yamada K, Kanda Y, Saito M, Eto M, et al. Impact of adiposity and plasma adipocytokines on diabetic angiopathies in Japanese Type 2 diabetic subjects. 2004;881–8.
22. Nakashima A, Yokoy K, Kawanami D, Ohk I. Association between resistin and fibroblast growth factor 23 in patients with type 2 diabetes mellitus. 2018;(March):1–7.
23. Ferreira MT. *Salles GF. Prognostic importance of baseline and serial glycated hemoglobin levels in high-risk patients with type 2 diabetes: the Rio de Janeiro Type. ,2* Diabetes Cohort Study: Mi. 2014.
24. Freemantle N, Danchin N, Vincent M, Home PD. Relationship of glycaemic control and hypoglycaemic episodes to 4-year cardiovascular outcomes in people with type 2. diabetes 2016:152-8.
25. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. 2012;7(8).
26. Banerjee D, Recio-mayoral A, Chitalia N, Kaski J. Clinical investigations insulin resistance, inflammation, and vascular disease in nondiabetic predialysis chronic kidney disease patients. 2011;365:360–5.
27. Caravaca F, Cerezo I, Macías R. Vinuesa EG De, Viejo CM, Villa J, et al. Insulin resistance in chronic kidney disease: its clinical characteristics and prognostic. significance 2010;30(6):661-8.
28. Sciacqua A, Marini MA, Hribal ML, Perticone F, Sesti G. Association of insulin resistance indexes to carotid intima–media thickness. 2013;8(1).
29. Study TB. The Bruneck Study. 2007;30(2).
30. Heine GH. Mineral metabolism in. heart disease 2015;24.
31. Freundlich M, Li YC, Quiroz Y, Bravo Y, Seeherunvong W, Faul C, et al. Paricalcitol downregulates myocardial renin–angiotensin and fibroblast growth factor expression and attenuates cardiac hypertrophy in uremic rats. 2014;27(May).

32. Panizo S, Barrio-vázquez S, Naves-díaz M, Carrillo-lópez N, Rodríguez I, Fernández-vázquez A, et al. Original articles Vitamin D receptor activation, left ventricular hypertrophy and myocardial fi brosis. 2013;(September):2735–44.
33. Kong J, Kim GH, Wei M, Sun T, Li G, Liu SQ, et al. Therapeutic effects of vitamin D analogs on cardiac hypertrophy in spontaneously hypertensive rats. Am J Pathol 2010;177:622-31.Internet. Available from, https://doi.org/10.2353/ajpath.2010.091292.
34. Thadhani R, Wenger J, Tamez H, Cannata J, Thompson BT. Andress D, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease 2015;2114.
35. Wang AY, Fang F, Chan J, Wen Y, Qing S, Chan IH, et al. Effect of paricalcitol on left ventricular mass and function in CKD — the OPERA trial. 2014;175–86.
36. Fujii H, Nakai K, Yonekura Y, Kono K, Goto S. The vitamin D receptor activator maxacalcitol provides cardioprotective effects in diabetes mellitus. 2015;499–507.
37. Zou J, Yu Y, Wu P, Lin F, Yao Y, Xie Y, et al. Serum phosphorus is related to left ventricular remodeling independent of renal function in hospitalized patients with chronic kidney disease. 2016;221:134-40.
38. Article O. Relationship between parathyroid hormone and cardiac. 2007;1507–12.
39. Soares AAS, Freitas WM, Japiass AVT, Quaglia LA, Santos SN, Pereira AC, et al. Enhanced parathyroid hormone levels are associated with left ventricle hypertrophy in very elderly men and women. 2015;9(9):697–704.
40. Moreno LO, Salvemini L, Mendonca C, Copetti M, Bonis C De, Cosmo S De, et al. Serum resistin and glomerular filtration rate in patients with type 2 diabetes. 2015;50:1–9.
41. Lim S, Kyeong B, Wook S, Kihara S, Funahashi T, Min Y, et al. Association of adiponectin and resistin with cardiovascular events in Korean patients with type 2 diabetes: the Korean Atherosclerosis Study (KAS). A 42-month prospective study. 2008;196:398–404.
42. Luc G, Empana J, Morange P, Arveiler D, Ferrieres J, Amouyel P, et al. Adipocytokines and the risk of coronary heart disease in healthy middle aged men: the PRIME Study. Int J Obes (Lond) 2009;34:118-26.Internet. Available from, https://doi.org/10.1038/ijo.2009.204.
43. Sheng CH, Du ZW, Song Y, Wu XD, Zhang YC, Wu M, et al. Human resistin inhibits myogenic differentiation and induces insulin resistance in myocytes. Biomed Res Int 2013;2013.
44. Luo Z, Zhang Y, Li F, He J, Ding H, Yan L, et al. Resistin induces insulin resistance by both AMPK-dependent and AMPK-independent mechanisms in HepG2 cells. Endocrine 2009;36:60-9.
45. Spoto B, Mattace-raso F, Sijbrands E, Pizzini P, Cutrupi S, Arrigo GD, et al. Resistin and all-cause and cardiovascular mortality: effect modi fi cation by adiponectin in end-stage kidney disease patients. 2013;(Cv):181–7.
46. Koch A, Gressner OA, Sanson E, Tacke F, Trautwein C. Serum resistin levels in critically ill patients are associated with inflammation, organ dysfunction and metabolism and may predict survival of non-septic patients. 2009;13(3):1–9.
47. Erer HB, Sayar N, Guvenc TS, Aksaray S, Yilmaz H. Altay S, et al. Prognostic value of serum resistin levels in patients with acute myocardial infarction 2014;55:181-6.
48. Wu X, Lin Y, Chen A, Hsu T, Wu Y, Lin H, et al. Prognostic significance of adipocytokines in systolic heart failure patients. 2012;1–8.
49. Park HK, Kwak MK, Kim HJ, Ahima RS. Linking resistin, inflammation, and cardiometabolic. diseases 2017:239-47.
50. Khera AV, Qamar A, Murphy SA, Cannon CP, Sabatine MS, Rader DJ. On-statin resistin, leptin, and risk of recurrent coronary events after hospitalization for an acute coronary syndrome (from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Study). Am J Cardiol 2015;116(5):694-8.Internet. Available from, https://doi.org/10.1016/j.amjcard.2015.05.038.
51. Park HK. Ahima RS. Resistin in rodents and humans 2013:404-14.
52. Zhang MH, Na B, Schiller NB, Whooley MA. Association of resistin with heart failure and mortality in patients with stable coronary heart disease: data from the Heart and Soul Study. 2011;17(1):24–30.
53. Kawamura R, Doi Y, Osawa H, Ninomiya T, Hata J, Yonemoto K, et al. Circulating resistin is increased with decreasing renal function in a general Japanese population: the Hisayama Study. March 2010:3236-40.
54. Ellington AA, Malik AR, Klee GG, Turner ST, Rule AD. Jr THM, et al. Association of plasma resistin with glomerular filtration rate and albuminuria in hypertensive adults 2015:708-15.