Atrial Natriuretic Peptide Deterioration Diabetic Nephropathy via Stimulating Secretion of Cytokines

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Abstract

Background: Atrial natriuretic peptide (ANP) refers to a cardiovascular and metabolic hormone that has been identified recently for chronic kidney disease (CKD) without diabetes. Cytokines (e.g., interleukin-6 (IL-6), tumor necrosis element-α (TNF-α) as well as adiponectin (ADP)) contribute to development of diabetes of type 2 (T2DM). The aim here was at investigating ANP and some cytokines extents for a systematic analysis of relationship level in T2DM nephropathy patients.

Methods: Plasma samples from T2DM patients (n=81) in accordance with albuminuria were split into normoalbuminuria (n=37), microalbuminuria (n=23) and macroalbuminuria (n=21), as collected after the consent was received. Based on enzyme-associated immunosorbent test, ANP, TNF-α, IL-6 and ADP in plasma underwent the quantification, and the data received the analysis for determining the correlation between ANP and cytokines among 3 cohorts.

Results: The present study reported that macroalbuminuria patients exhibited higher plasma levels of ANP, TNF-α, IL-6, ADP, serum creatinine (Cr), blood urea nitrogen (BUN) and duration of diabetes mellitus (DM) than the cases subjected to normoalbuminuria and microalbuminuria. Plasma ANP level was significantly associated with TNF-α, IL-6 and ADP, independently of duration of DM and BUN.

Conclusion: Elevated serum ANP levels are likely to impact the metabolism of adipose tissue and inflammation which involved in the pathogenesis and progression of DN.

Background

Diabetic nephropathy (DN) refers to one considerable microvascularly-related diabetes complication and takes up at least 50% of end-stage renal disease (ESRD) [1, 2]. Diagnosis of DN as soon as possible is conducive to preventing diabetic kidney diseases from progressing.

By analyzing fundamental cytokines, targets or markers may be revealed to identify and treat T2DM patients, particularly those predictive of DN. Atrial natriuretic peptide (ANP) refers to a member of family of cardiac- and vascular derived hormones, primarily secreted from atrial or ventricular involved in the control of increased volume or elevated blood pressure [3]. ANP has been recently identified as act on blood vessel and adrenal gland, exhibiting natriuretic and vasodilating properties and critically controlling volume homeostasis and blood pressures [4, 5]. Several analyses are carried out, demonstrating the elevated serum levels of natriuretic peptide in cases developing chronic kidney disease (CKD) under the complication of renal functions under impairment. In the mentioned reports, the mentioned peptides seem to be marking elements of renal function reduction or CKD progressing [6, 7]. ANP also participates in adipose metabolic pathways [8]. Adipose tissue is known as an important endocrine tissue that secretes numerous biologically active proteins and many cytokines by adipocytes and other adipose tissue stromal cells, respectively [9]. Adiponection (ADP) refers to a specific protein under the exclusive secretion of adipose tissues and appears to act as a hormone which could down regulate inflammatory responses in vitro. Likewise, decreased ADP shows an accompany with T2DM and the relevant macrovascular complication, as well as insulin resistance [10, 11]. However, recent studies have pointed out that the levels of urinary or serum ADP is both elevated in primary nephrotic syndrome and DN patients [12, 13]. ANP may regulate adipocyte metabolism including ADP through lipolysis, lipid oxidation, and

adipocyte browning or directly influence on macrophage [14–16]. Several inflammation cytokines (e.g., interleukin-6 (IL-6) and tumor necrosis element-α (TNF-α)) refer to risks-related elements for the damages of glomerular and vascular endothelial cells, attempting to improve urinary albumin in T2DM cases.

The effect exerted by ANP on T2DM albuminuria patients was analyzed. Moreover, the concentrations of ADP along with TNF-α and IL-6 received the measuring process to elucidate the interaction, if any, of the mentioned cytokines and ANP in patients stratified by albuminuria.

Methods

According to the Department of Endocrinology of Nanjing First Hospital, Nanjing Medical University, China, the present study was carried out from May to August 2016. 81 T2DM cases subjected to different stages of DN were involved according to the guidelines for chronic kidney disease[17]: 21 with macroalbuminuria (Macro-MA cohort), 23 with microalbuminuria (Micro-MA cohort) and37 with normoalbuminuria (Nor-MA cohort). Macroalbuminuria, microalbuminuria and Normoalbuminuria received the definition of urine albumin excretion amount (UAE) > 300 mg/24 h, 30–300 mg/24 h and < 30 mg/24 h [17], separately.

The exclusion standards consist of: (1) cases exhibiting a history of overt cerebrovascular accident (myocardial infarction, angina pectoris and stroke); (2) cases subjected to severe non-regulated high blood pressure gaining the definition of systolic pressure of blood > 160 mmHg/ diastolic blood pressure > 100 mmHg; (3) cases subjected to severe dyslipidemia (total cholesterol > 400 mg/d; (4) cases subjected to urine tract infection and any other acute inflammation or infection; (5) cases subjected to kidney diseases except DN and using anticonvulsant drugs, anti-inflammatory drugs or nephrotoxic drug users; (6) cases exhibiting diagnosed liver failure, malignancy under the previous diagnosis; (7) pregnant women, lactation; (8) positivity for islet cell autoantibodies indicating possibility of type 1 diabetes mellitus; (9) patients treated with thiazolidinediones which are known to partly increase plasma ADP level.

Physical examinations were performed as measurement of blood pressure, height, weight and other anthropometric parameters. Samples of venous blood received the drawing process in all patients when the 8 h fasting and treating process were completed in a separate manner. Biochemical and hematological properties received the determination with routine technologies with one analyzing element automation. Blood received the collection from 4 ml EDTA containing element and the centrifugation in 30 min based on 3000 rpm for 10 min. Serum samples underwent the subsequent storing process inside aliquots with no preservatives at −80 °C for 3 months on average. Such process stopped in advance to cytokines study. Plasma levels of ANP, ADP, IL-6 and TNF-α received the measuring process based on human enzyme-associated immune sorbent testing process (ELISA) tools with commercial availability (ANP: catalogue number bsk00431, Bioss, Burlington, ON, Canada; ADP: catalogue number bsk00199, Bioss, Burlington, ON, Canada; IL-6: catalogue number bsk00040, Bioss, Burlington, ON, Canada; TNF-α: catalogue number bsk00162, Bioss, Burlington, ON, Canad). The detection limit for ANP, ADP, IL-6 and TNF-α was 10 ng/L, 30 ug/L, 2 ng/L and 8 pg/L, separately. The intra-test and intertest change coefficients took up 5% and 10%, separately.

Body mass index (BMI) was calculated as weight (kg)/square of height.

Statistical Analysis

Based on Windows 20.0 statistical software, data received the analysis based on SPSS (Statistical Package for Social Sciences). In terms of continuous normal data, Mean ± SD values were reported; otherwise, median (interquartile range) received the report. For assessing the correlation of Macro-MA and Nor-MA cohorts based on categorical variables, the authors performed Chi-square testing processes. This study conducted one ANOVA testing for comparing differences of mean between 3 cohorts. In addition, the authors employed the Kruskal-Wallis testing for comparing diversifications of mean of three cohorts based on normal distributing process. Correlations were tested by conducting regression analysis. For determining the relationship between numerical variables for normally distributed cohorts, Pearson correlation analysis was used, and Spearman test was used for abnormally distributed cohorts. Logistic regression analysis was conducted to assess the associations between ANP level and the other parameters assessed. A two-tailed *p* values < 0.05 were considered exhibiting significance.

Results

According to Table 1, the individuals in 3 cohorts were well matched for age and gender composition. SBP was significantly higher in Macro-MA cohort than other 2 cohorts, while DBP was comparable between 3 cohorts. No differences were identified in alanine transarninase (ALT), aspartate transaminase (AST), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Na, K and uric acid (UA) between 3 cohorts. Naturally, glycosylated hemoglobin (HbA1c) levels of all study patients were above normal values, whereas HbA1c was lower in Macro-MA cohort than other two cohorts ($p < 0.05$). Moreover, glucose in Macro-MA cohort was 6.35 (5.09, 8.08) mmol/L, which was distinctly lower than other two cohorts. Macroalbuminuria patients showed remarkably higher duration of DM, Cl, serum creatinine, urea, but low plasma albumin levels ($p < 0.05$ in all comparisons).

Table 1
General clinical profiles between 3 groups

Variable	Nor-MA	Micro-MA	Macro-MA	*P* value
N	37	23	21	-
Men (%)	23(62.2)	11(47.82)	11(52.38)	0.533[a]
Age (years)	61.32(11.69)	66.17(13.41)	66.10(8.68)	0.181[b]
BMI (kg/m^2)	23.24(20.85,26.86)	24.24(21.97,26.67)	24.78(22.95,27.24)	0.709[b]
Duration (years)	3.40(3.49)	10.13(6.61)	16.52(7.90)**	< 0.001[a]
SBP (mmHg)	127(13)	133(17)	139(17)**	0.025[a]
DBP(mmHg)	78(7)	77(8)	79(8)	0.522[a]
UAE (mg/24 h)	11.94(7.44,21.09)	96.90(54.78,168.66)	1155.77(854.69,1575.00)**	< 0.001[a]
HbA1c (%)	8.50(7.00,10.55)	9.10(7.00,10.20)	7.10(6.15,8.20)*	0.018[b]
ALT(IU/L)	23.16(11.78)	30.09(40.82)	19.19(9.14)	0.299[a]
AST(IU/L)	27.57(19.13)	30.83(26.49)	20.82(13.53)	0.256[a]
TC(mmol/L)	4.78(3.80,5.35)	4.45(3.22,5.53)	5.26(3.84,6.14)	0.286[b]
TG(mmol/L)	1.88(1.66)	2.18(2.05)	2.71(2.43)	0.317[a]
HDL-C(mmol/L)	1.15(0.98,1.35)	1.05(0.92,1.36)	1.05(0.87,1.24)	0.421[b]
LDL-C(mmol/L)	2.54(1.91,3.03)	2.27(1.37,2.84)	2.95(1.80,3.50)	0.229[b]
BUN(mmol/L)	6.02(1.26)	7.28(3.84)	11.26(6.41)**	< 0.001[a]

Continuous variables were expressed as mean (standard deviation) and non-normally distributed variables were expressed as median (interquartile range). An ANOVA test was used to to compare differences of mean between 3 groups ([a]). The Kruskal-Wallis test was used to compare differences of mean between 3 groups with normal distribution ([b]).

*P < 0.05 compared with control group,** P < 0.01 compared with control group.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAE, urinary albumin excretion; HbA1c, glycosylated hemoglobin; ALT, alanine transarninase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Cr, plasma creatinine; TC, total cholesterol; TG, triglycerides; UA, uric acid; ALB, plasma albumin.

Variable	Nor-MA	Micro-MA	Macro-MA	*P* value
Cr(umol/L)	68.34(21.80)	86.73(57.11)	175.38(109.76)**	< 0.001[a]
Na(mmol/L)	141.80(139.45,142.85)	140.70(139.60,142.60)	141.70(139.10,144.15)	0.610[b]
K(mmol/L)	3.83(3.60,3.99)	3.87(3.56,4.30)	3.77(3.34,4.36)	0.728[b]
Cl(mmol/L)	101.90(100.95,102.30)	102.80(101.10,104.90)	104.90(102.15,107.35)**	< 0.001[b]
UA(umol/L)	353.00(251.50,428.00)	298.00(263.00,465.00)	355.00(306.00,476.00)	0.415[b]
ALB(g/L)	40.50(38.60,40.75)	41.40(36.50,43.60)	34.80(30.70,38.05)**	< 0.001[b]
Continuous variables were expressed as mean (standard deviation) and non-normally distributed variables were expressed as median (interquartile range). An ANOVA test was used to to compare differences of mean between 3 groups ([a]). The Kruskal-Wallis test was used to compare differences of mean between 3 groups with normal distribution ([b]).				
*$P < 0.05$ compared with control group,**$P < 0.01$ compared with control group.				
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAE, urinary albumin excretion; HbA1c, glycosylated hemoglobin; ALT, alanine transarninase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Cr, plasma creatinine; TC, total cholesterol; TG, triglycerides; UA, uric acid; ALB, plasma albumin.				

As revealed from the results here, the serum ANP level in Macro-MA cohort was significantly higher than the other two cohorts (11.25 ± 4.05 ng/L and 13.58 ± 6.43 ng/L in cases subjected to normoalbuminuria and microalbuminuria, respectively). Interestingly, compared to cases subjected to normoalbuminuria, macroalbuminuria patients had apparently higher serum ADP ($p < 0.001$). Furthermore, the levels of TNF-α, IL-6 also increased as nephropathy progressed, with median serum TNF-α levels of 13.49 pg/mL in the normoalbuminuric cohort, 15.22 pg/mL in the Micro-MA cohort, and 18.28 pg/mL in the Macro-MA cohort. The median serum levels of IL-6 was 2.13 ng/L in the normoalbuminuric cohort, 2.20 ng/L in the Micro-MA cohort, and 3.21 ng/L in the Macro-MA cohort (Table 2).

Table 2
Plasma cytokines levels of patients according to the albuminuria categories

Variable	Nor-MA	Micro-MA	Macro-MA
ANP(ng/L)	11.25(4.05)	13.58(6.43)	19.20(13.43)**
TNF-α (pg/mL)	13.49(4.67)	15.22(7.57)	18.28(13.50)*
ADP (ug/L)	4.96(2.52)	5.55(2.74)	7.96(6.16)**
IL-6(ng/L)	2.13(1.18)	2.20(1.35)	3.21(2.95)*
*P< 0.05 compared with control group,**P< 0.01 compared with control group.			
ANP, atrial natriuretic peptide; ADP, adiponection; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.			

The authors assessed the mentioned variables based on multiple variates-based analyzing processes, Table 3 lists the relevant results. Specific to the entire subject group, Pearson's or Spearman linear correlating process displayed a noticeable positive relationship of ANP and UAE (r = 0.235, p = 0.035), BUN (r = 0.235, p = 0.034), as well as plasma ADP (r = 0.772, p < 0.001), (Fig. 1), IL-6 (r = 0.816, p < 0.001), (Fig. 2) and TNF-α (r = 0.876, p < 0.001), (Fig. 3). An important correlation was noted between ANP and duration of DM based on simple regression study on research subjects. The authors reported noticeably negative relationship of ANP and plasma albumin (r=-0.267, p = 0.016). This study reported not any noticeable correlations of ANP and other variables covering BP, lipid profiles, glucose, liver enzyme and urea acid (Table 3). In univariate analysis, all the parameters listed in Table 4 received the judging process as displaying noticeable associations to DN developing process. In Model 1, because duration of diabetes was an independent risk element, we excluded it from the analysis, identifying all the parameters shown in this model as significant elements for DN development. In Model 2, the authors covered duration of diabetes, results showed that both UAE and BUN turned out to be not significant; plasma ANP and DM duration were correlated. For this reason, the authors considered duration of DM a powerful cofounder in the relationship between ANP and DN development. Furthermore, ADP, TNF-α and IL-6 still correlated independently with ANP (p < 0.05) after adjustment for duration of diabetes and BUN.

Table 3
Univariate linear regression analysis between serum ANP and the clinical parameters

Variable	r	*P*
Age	0.034	0.760[a]
BMI	0.109	0.334[b]
Duration	0.285	0.010 [a]
SBP	0.066	0.559[a]
DBP	0.087	0.442[a]
HbA1c	-0.003	0.978[b]
UAE	0.235	0.035[b]
TC	0.072	0.552[b]
TG	0.106	0.346[a]
HDL-C	-0.023	0.838[b]
LDL-C	0.034	0.764[b]
BUN	0.235	0.034[a]
Cr	0.198	0.076[a]
UA	0.123	0.274[b]
ALB	-0.267	0.016[b]
ADP	0.772	< 0.001[a]
IL-6	0.816	< 0.001[a]
TNF-α	0.876	< 0.001[a]

[a] Pearson test

[b] Spearman test

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UAE, urinary albumin excretion; HbA1c, glycosylated hemoglobin; ALT, alanine transarninase; AST, aspartate transaminase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Cr, plasma creatinine; BUN, blood urea nitrogen; TC,total cholesterol; TG, triglycerides; UA, uric acid; ALB, plasma albumin; ANP, atrial natriuretic peptide; ADP, adiponection; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Table 4
Multiple regression model for the determinants of serum ANP

Independent variable	Model 1		Model 2	
	β	*P*	β	*P*
Duration (years)	-	-	0.049	0.044
UAE (mg/24 h)	0.150	0.033	0.059	0.045
TNF-α (pg/mL)	0.528	< 0.001	0.519	< 0.001
ADP (ug/L)	0.233	0.001	0.224	0.001
IL-6 (ng/L)	0.255	0.006	0.233	0.005
BUN(mmol/L)	0.127	0.032	0.041	0.592

UAE, urinary albumin excretion; ANP, atrial natriuretic peptide; ADP, adiponection; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; BUN, blood urea nitrogen.

Discussion

To our knowledge, DN has been commonly confirmed by clinical symptoms. A large percentage of T2DM is unconventionally assessed with a renal biopsy and even though pathological diagnosis. T2DM cases subjected to albuminuria fail to diagnose to DN in clinical promptly. Moreover, progressive renal lesions in DN are considered difficult to reverse. Therefore, it is imperative to gain insights into albuminuria, and the subsequent analysis and exploration of new targets or predictive markers for DN. Given the information acquired by the authors, the present study initially demonstrates that serum inflammatory cytokines display an independent association with ANP in DN. As our excluded criteria, we ruled out cases subjected to any acute inflammation or infection, renal insufficiency, serious cardiac insufficiency and treated with thiazolidinediones. Therefore, we have tried to eliminate confounding elements which probably interfere with the association between ANP and inflammation cytokines.

The level of ANP was augmented in Macro-MA cohort opposed to Nor-MA cohort ($p < 0.001$). Moreover, the level of inflammatory cytokines was elevated obviously in Macro-MA cohort, which was accordance with several recent studies [18–20]. Plasma ANP extents were reported here displaying positive relationships to UAE, BUN, IL-6, TNF-α and ADP as well as negatively correlated with plasma albumin by simple regression. When the influence exerted by other variables based on partially-related correlation study, the existing relationships of ANP and duration of DM, IL-6, TNF-α and ADP level remained significantly, but not the relationship between ANP and BUN or UAE. To be specific, ADP, IL-6 and TNF-α are likely to be particularly important since the relationship of the ANP plasma extents and DN developing process was determined by inflammatory response.

ANP is a cardiac hormone provides a negative feedback to elevated blood pressure and fluid volume [3]. Robert et al. [21] proved ANP may well improve intravascular protein's glomerular permeability in the glomerulus though infusion of synthetic human ANP in cases subjected to nephrotic syndrome. ANP dilate afferent arteriolar and constrict efferent arteriolar producing an increase in the glomerular capillary pressure and lead to a rise in fractional excretion of proteins [22]. For the foregoing reasons, ANP may induce microalbuminuria.

According to Desai et al. [23], the higher the plasma level of ANP was, renal function will be deteriorated more rapidly. We did not expect ANP was elevated with DN development, whereas there are several possible explanations for such finding. First, reduction of renal function with disease course may be required to be considered as capable of elevating fluid volume and also because left atrial pressure induces augments secretions of ANP. Second, the one major metabolic pathways of ANP involved binding to clearance receptors (NPR-C) [24]. As revealed from one recent study, the number of NPR-C on platelets in elderly subjects decreased, which could be associated with a reduction the synthesis of this receptor or a delayed recycle to the cell surface [25]. Third, ANP was knocked down by the neutral endopeptidase (NEP), the enzyme capable of being expressed in kidney. NEP expression in renal tissue showed the down-regulation among chronic renal failure patients. The mentioned eventually result in decreased clearance of ANP from circulation. Thus, ANP may participate in DN development. Nevertheless, precise mechanisms remain unclear.

ANP is capable of regulating lipolysis and lipid mobilization in humans. Moreover, it might regulate adipose tissue inflammation by regulating the secretion of inflammation cytokines [26, 27]. The elevation levels of TNF-α, IL-6 and ADP here showed strong positively correlations with ANP and the degree of albuminuria, abiding by existing studies [18, 19]. As revealed from one existing study, adipocytes probably expressed all components of the ANP-signaling pathway [16]. ANP inducted secretion of IL-6 and TNF-α via the guanylate cyclase-coupled A receptor (NPR-A) with mRNA coding expressed on macrophages [28]. Activation of the NPR-A receptor stimulates a rise in cGMP levels, activating protein kinase G; as a result, lipolysis is stimulated to IL-6 and TNF-α productions. ADP, a “conducive” adipokine withdraw inflammation, is reduced in cases subjected to diabetes, and high ADP levels were associated with a lower risk of developing T2DM [29–31]. Nerveless, ADP concentrations are higher in cases subjected to increasing albuminuria especially in Macro-MA cohort and positive predict process of this disease [32]. ADP is known to activate via the AMP-activated protein kinase, so dose ANP in adipocytes [33]. The similar effect was also indicated among healthy people, demonstrating that ANP raises ADP in dose-dependent manner [34]. The phenomenon complies with the possible mechanism that ANP directly preserving ADP counteracted ANP-induced lipolysis. One existing study also reported in a small clinical study that decompensated heart failure patients having undergone therapeutic ANP infusions had increased plasma levels of total and high molecular weight ADP [35]. As reported by recent studies, during DN development, increased production and excretion of inflammation cytokines result in aggravated glomerular hypertrophy and disappeared podocyte foot, which are activated and contribute to deteriorate kidney impairment [36]. As a result, ANP may promote progression of DN by stimulating secretion of inflammation cytokines. Further investigation ANP receptor antagonist or enzymes inhibitors can significantly improve and postpone the progress of DN.

Notably, HbA1c level was more decreased in Macro-MA than the other 2 cohorts. Some of the mentioned reasons could be explained that the patients who with longer duration of DM and with diabetic complications have stronger consciousness in blood glucose management. Besides, as suggested from a previous study, ANP may impact etiology of diabetes primarily due to inhibiting effect on glucagon secretion [37]. Moreover, Suzanne et al.[38] conducted the isolation of pancreatic islets in adult mice and showed that ANP enhanced insulin secretion under the stimulation of glucose and triggered β-cell growth.

This study has some limitations. First, the cross-sectionally-related designing analysis on baseline data of a cohort analysis and the restricted amount belonging to each cohort are likely to have causal relationship, and

more randomization-based and further analyses containing larger samples require in-depth explorations. Second, we cannot completely exclude the possibility that ANP influenced on clearance of renal or hepatic cytokines. Finally, only plasma cytokines have been measured, but at what stages ANP and other cytokines levels in urine were not investigated, probably help interpret the result here.

Conclusion

To sum up, increased circulating extents of plasma ANP, displaying relationships to duration of DM, could precede type 2 diabetic kidney disease developing process with no noticeable cardiovascularly-located disease, revealing one likely effect exerted by such bioactive peptide in monitoring DN developing process at early phase. ANP may exert a potential endocrine function though adipose tissue to regulate inflammatory cytokines amounts participating in pathogenesis and progression of DN.

Abbreviations

ANP, Atrial natriuretic peptide; CKD, chronic kidney disease; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; ADP, adiponectin; T2DM, type 2 diabetes; Cr, serum creatinine; BUN, blood urea nitrogen ; DM, duration of diabetes mellitus; CKD, chronic kidney disease; UAE, urine albumin excretion; ALT, alanine transarninase ; AST, aspartate transaminase; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol ; UA, uric acid; HbA1c, glycosylated hemoglobin.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Nanjing First Hospital, Nanjing Medical University with the approval number 2016-Research-28. Due to the retrospective nature of the study, the requirement to obtain informed consent was waived.

Consent to publish

Not applicable.

Availability of data and materials

Our data will not be shared due to it was involved in individual privacy and needed further study.

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

CL, Qi L and Qian L designed experiments. CL, Qi L and XF performed experiments. CL clinically managed the patient, conducted literature review and wrote the manuscript. Qi Li helped with the acquisition and interpretation of data and with manuscript revisions. Ashley shane vadamootoo helped to polish the language. CL and Qi L analyzed the data. Qian L and JZ guaranteed this work and provide academic guidance. All authors read and approved the final manuscript.

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References

1. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T: **Diabetic nephropathy in Type 1 (insulin-dependent) diabetes: an epidemiological study**. *Diabetologia* 1983, **25**(6):496-501.
2. Ritz E, Rychlik I, Locatelli F, Halimi S: **End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1999, **34**(5):795-808.
3. Ogawa T, de Bold AJ: **The heart as an endocrine organ**. *Endocrine connections* 2014, **3**(2):R31-44.
4. Levin ER, Gardner DG, Samson WK: **Natriuretic peptides**. *The New England journal of medicine* 1998, **339**(5):321-328.
5. Brunova J: **[Endocrine diseases and diabetes]**. *Casopis lekaru ceskych* 2004, **143**(8):507-511.
6. Dieplinger B, Mueller T, Kollerits B, Struck J, Ritz E, von Eckardstein A, Haltmayer M, Kronenberg F, Group MS: **Pro-A-type natriuretic peptide and pro-adrenomedullin predict progression of chronic kidney disease: the MMKD Study**. *Kidney international* 2009, **75**(4):408-414.
7. Spanaus KS, Kronenberg F, Ritz E, Schlapbach R, Fliser D, Hersberger M, Kollerits B, Konig P, von Eckardstein A, Mild-to-Moderate Kidney Disease Study G: **B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the Mild-to-Moderate Kidney Disease Study**. *Clinical chemistry* 2007, **53**(7):1264-1272.
8. Wang Y, Xu L, Yuan L, Li D, Zhang Y, Zheng R, Liu C, Feng X, Li Q, Li Q *et al*: **Sodium-glucose co-transporter-2 inhibitors suppress atrial natriuretic peptide secretion in patients with newly diagnosed Type 2 diabetes**. *Diabetic medicine : a journal of the British Diabetic Association* 2016, **33**(12):1732-1736.
9. Kershaw EE, Flier JS: **Adipose tissue as an endocrine organ**. *The Journal of clinical endocrinology and metabolism* 2004, **89**(6):2548-2556.

10. Rasouli N, Kern PA: **Adipocytokines and the metabolic complications of obesity**. *The Journal of clinical endocrinology and metabolism* 2008, **93**(11 Suppl 1):S64-73.
11. Kawano J, Arora R: **The role of adiponectin in obesity, diabetes, and cardiovascular disease**. *Journal of the cardiometabolic syndrome* 2009, **4**(1):44-49.
12. Bakkaloglu SA, Soylemezoglu O, Buyan N, Funahashi T, Elhan AH, Peru H, Fidan K, Yilmaz S, Hasanoglu E: **High serum adiponectin levels during steroid-responsive nephrotic syndrome relapse**. *Pediatric nephrology* 2005, **20**(4):474-477.
13. Koshimura J, Fujita H, Narita T, Shimotomai T, Hosoba M, Yoshioka N, Kakei M, Fujishima H, Ito S: **Urinary adiponectin excretion is increased in patients with overt diabetic nephropathy**. *Biochemical and biophysical research communications* 2004, **316**(1):165-169.
14. Costello-Boerrigter LC, Burnett JC, Jr.: **A new role for the natriuretic peptides: metabolic regulators of the adipocyte**. *Journal of the American College of Cardiology* 2009, **53**(22):2078-2079.
15. Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessi-Fulgheri P, Zhang C, Takahashi N, Sarzani R, Collins S: **Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes**. *The Journal of clinical investigation* 2012, **122**(3):1022-1036.
16. Moro C, Klimcakova E, Lolmede K, Berlan M, Lafontan M, Stich V, Bouloumie A, Galitzky J, Arner P, Langin D: **Atrial natriuretic peptide inhibits the production of adipokines and cytokines linked to inflammation and insulin resistance in human subcutaneous adipose tissue**. *Diabetologia* 2007, **50**(5):1038-1047.
17. Mogensen CE: **Practice guidelines for chronic kidney disease**. *Annals of internal medicine* 2004, **140**(11):933-934; author reply 934-935.
18. Lampropoulou IT, Stangou M, Papagianni A, Didangelos T, Iliadis F, Efstratiadis G: **TNF-alpha and microalbuminuria in patients with type 2 diabetes mellitus**. *Journal of diabetes research* 2014, **2014**:394206.
19. Shikano M, Sobajima H, Yoshikawa H, Toba T, Kushimoto H, Katsumata H, Tomita M, Kawashima S: **Usefulness of a highly sensitive urinary and serum IL-6 assay in patients with diabetic nephropathy**. *Nephron* 2000, **85**(1):81-85.
20. Choudhary N, Ahlawat RS: **Interleukin-6 and C-reactive protein in pathogenesis of diabetic nephropathy: new evidence linking inflammation, glycemic control, and microalbuminuria**. *Iranian journal of kidney diseases* 2008, **2**(2):72-79.
21. Zietse R, Schalekamp MA: **Effect of synthetic human atrial natriuretic peptide (102-126) in nephrotic syndrome**. *Kidney international* 1988, **34**(5):717-724.
22. Ballermann BJ, Brenner BM: **Atrial natriuretic peptide and the kidney**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1987, **10**(1 Suppl 1):7-12.
23. Desai AS, Toto R, Jarolim P, Uno H, Eckardt KU, Kewalramani R, Levey AS, Lewis EF, McMurray JJ, Parving HH *et al*: **Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2011, **58**(5):717-728.
24. Misono KS: **Natriuretic peptides and their receptors**. *The FEBS journal* 2011, **278**(11):1791.
25. Giannessi D, Andreassi MG, Del Ry S, Clerico A, Colombo MG, Dini N: **Possibility of age regulation of the natriuretic peptide C-receptor in human platelets**. *Journal of endocrinological investigation* 2001, **24**(1):8-

16.

26. Vaz Perez A, Doehner W, von Haehling S, Schmidt H, Zimmermann AV, Volk HD, Anker SD, Rauchhaus M: **The relationship between tumor necrosis factor-alpha, brain natriuretic peptide and atrial natriuretic peptide in patients with chronic heart failure**. *International journal of cardiology* 2010, **141**(1):39-43.
27. Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, Okazaki H, Asai M, Nagamachi Y, Maeda N *et al*: **Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure**. *Journal of the American College of Cardiology* 2009, **53**(22):2070-2077.
28. Kiemer AK, Hartung T, Vollmar AM: **cGMP-mediated inhibition of TNF-alpha production by the atrial natriuretic peptide in murine macrophages**. *Journal of immunology* 2000, **165**(1):175-181.
29. Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N: **Adipokines and risk of type 2 diabetes in older men**. *Diabetes care* 2007, **30**(5):1200-1205.
30. Li S, Shin HJ, Ding EL, van Dam RM: **Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis**. *Jama* 2009, **302**(2):179-188.
31. Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, Hoogeveen RC, Heiss G: **Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study**. *Diabetes* 2004, **53**(9):2473-2478.
32. Ran J, Xiong X, Liu W, Guo S, Li Q, Zhang R, Lao G: **Increased plasma adiponectin closely associates with vascular endothelial dysfunction in type 2 diabetic patients with diabetic nephropathy**. *Diabetes research and clinical practice* 2010, **88**(2):177-183.
33. Souza SC, Chau MD, Yang Q, Gauthier MS, Clairmont KB, Wu Z, Gromada J, Dole WP: **Atrial natriuretic peptide regulates lipid mobilization and oxygen consumption in human adipocytes by activating AMPK**. *Biochemical and biophysical research communications* 2011, **410**(3):398-403.
34. Birkenfeld AL, Boschmann M, Engeli S, Moro C, Arafat AM, Luft FC, Jordan J: **Atrial natriuretic peptide and adiponectin interactions in man**. *PloS one* 2012, **7**(8):e43238.
35. Tanaka T, Tsutamoto T, Sakai H, Nishiyama K, Fujii M, Yamamoto T, Horie M: **Effect of atrial natriuretic peptide on adiponectin in patients with heart failure**. *European journal of heart failure* 2008, **10**(4):360-366.
36. Barutta F, Bruno G, Grimaldi S, Gruden G: **Inflammation in diabetic nephropathy: moving toward clinical biomarkers and targets for treatment**. *Endocrine* 2015, **48**(3):730-742.
37. Verspohl EJ, Bernemann IK: **Atrial natriuretic peptide (ANP)-induced inhibition of glucagon secretion: mechanism of action in isolated rat pancreatic islets**. *Peptides* 1996, **17**(6):1023-1029.
38. You H, Laychock SG: **Atrial natriuretic peptide promotes pancreatic islet beta-cell growth and Akt/Foxo1a/cyclin D2 signaling**. *Endocrinology* 2009, **150**(12):5455-5465.

Figures

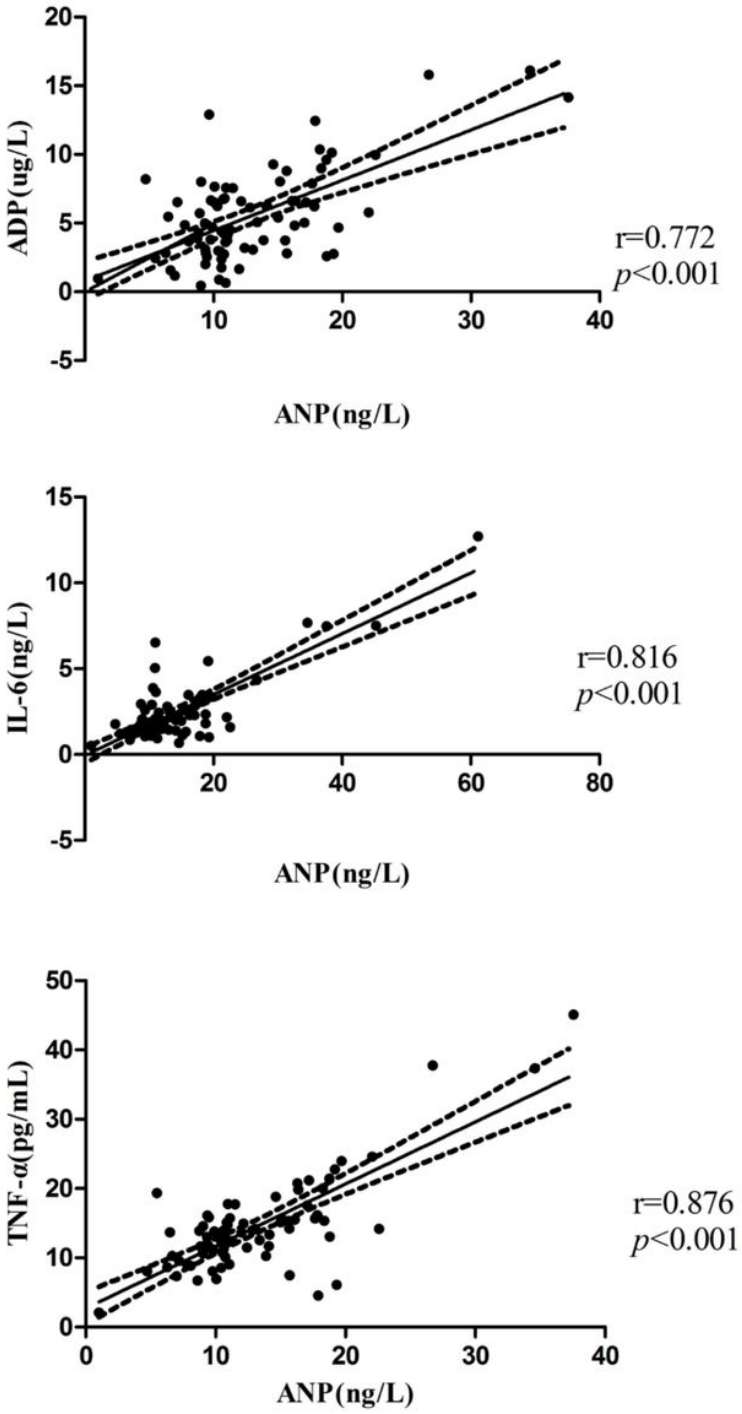

Figure 1

Correlation between ANP and serum ADP in patients with T2DM Correlation between ANP and serum IL-6 in patients with T2DM Correlation between ANP and serum TNF-α in patients with T2DM