THE EXPRESSION OF MICRORNA-21 AND MICRORNA-155 CORRELATES WITH NOCTURNAL HYPERTENSION IN CHRONIC KIDNEY DISEASE PATIENTS

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Introduction and objectives

- Emerging evidence indicates that microRNA play important role in regulation of blood pressure (BP).
- Chronic kidney disease (CKD) patients are at increased risk of hypertension, diagnozed in up to 85% of population [1].
- Patients with CKD tend to present abnormal circadian BP rhythm with the night-time BP increase [2-7]
- Angiotensin II acting via angiotensin II receptor type 1 (AGTR1) constitutes one of the prohypertensive mediators.
- MiR-155 has been recently proven to negatively regulate the expression of AGTR1[8].
- It has been reported that miR-21 is associated with decrease in NO production and eNOS levels as well as enhances lymphocyte T response [9-10].
- To date, the relationship between the miR-155 and miR-21 expression and the blood pressure values in CKD patients has not been established.

Methods

- Prospective, single-centre study
- 90 patients with stable CKD at the stage 2-5, including 25 KTx recipients, (47% M) and 26 healthy age-and sex-matched control subjects (50% M) with normal BP proven by ABPM
- Quantification of plasma miRNA with the use of realtime quantitative polymerase chain reaction (RT qPCR).
- Relative expression calculated using the delta delta Ct method vs. endogenuous control U6 snRNA.
- 24-hour ambulatory blood pressure measurement performed in each patient and control subject with SpaceLab Medical recorders
- All the factors mentioned in table 1 were evaluated in univariate and multivariate regression models.

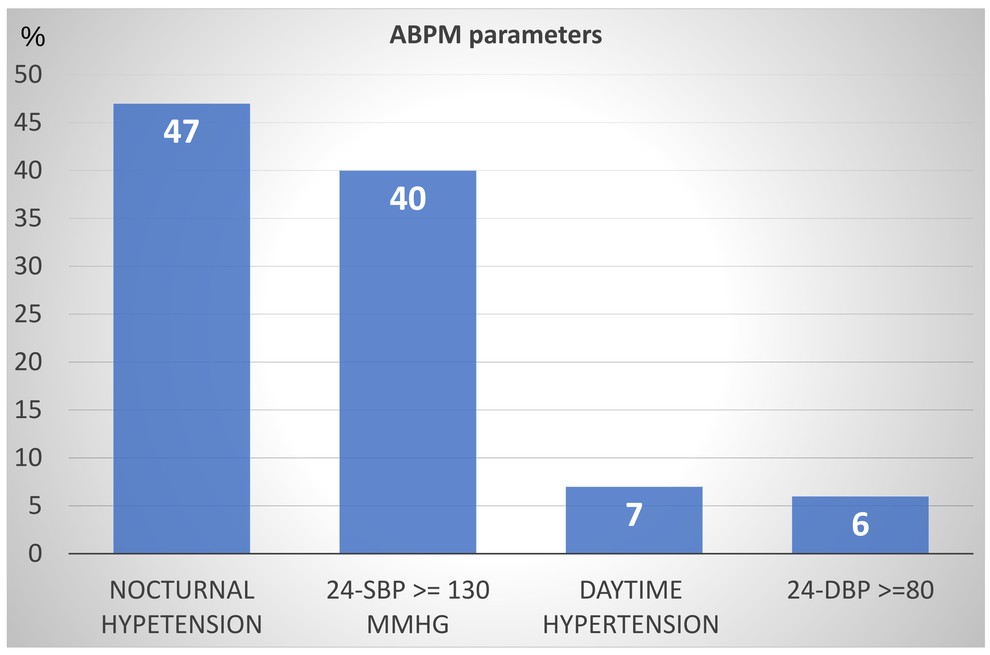

Fig. 1 Abnormal BP parameters according to ABPM, data shown as percentage.

Results

- miRNA-155 and miRNA-21 levels were upregulated in CKD pts compared to healthy control subjects with median relative expression levels 2.92 (Q1-Q3: 1.34-5.58) and 2.55 (Q1-Q3: 1.27-4.56) respectively.
- In the subgroup of KTx recipients, miRNA expression was not significantly different: 2.09 (Ktx) vs 2.97 (other CKD pts), p=0.37 for miR-21 and 2.32 vs 3.01, p=0.83 for miR-155 in U Mann-Whitney test.
- Patients with nocturnal hypertension (HTN) did not differ significantly in terms of GFR (p=0.35) and age (p=0.11) than the rest of CKD pts and were treated with 2.85 antihypertensive agents on average (vs. 2.12 in the rest of the group, p = 0.059).
- Pts on alpha-blockers presented significantly higher expression of miR-21 (4.6, 3.91-7.72), p=0.02 and miR-155 (4.71, 4.33-7.67), p=0.024. And those patients did not differ in terms of age and GFR than the rest.

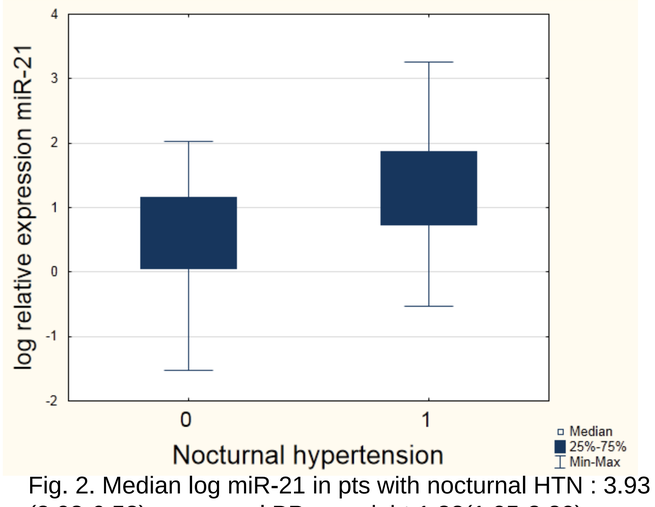

Fig. 2. Median log miR-21 in pts with nocturnal HTN : 3.93 (2.08-6.52) vs. normal BP overnight 1.82(1.05-3.20), p = 0.001.

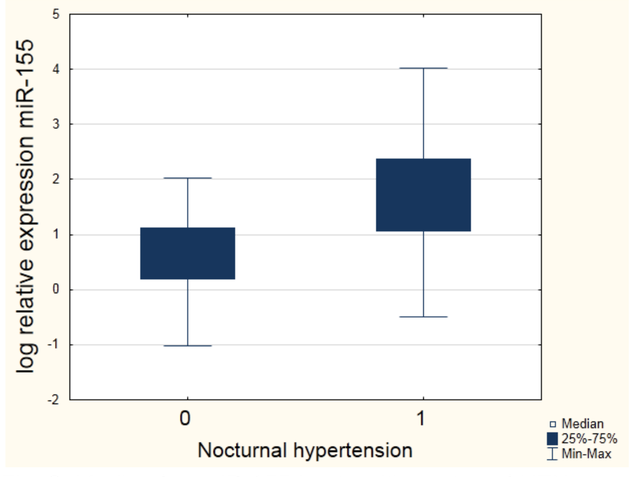

Fig. 3. Median log miR-155 in pts with nocturnal HTN 4.04 (2.92-10.8) vs. normal BP overnight 2.01 (1.21 -3.07), p = 0.001.

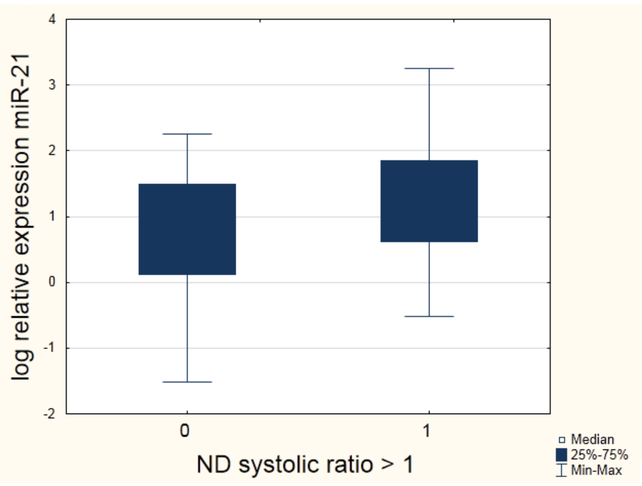

Fig. 4. Median log miR-21 in pts with night-day SBP ratio ≥1 3.77 (1.85-6.33) vs. night-day SBP < 1 2.34 (1.12- 4.42), p = 0.04

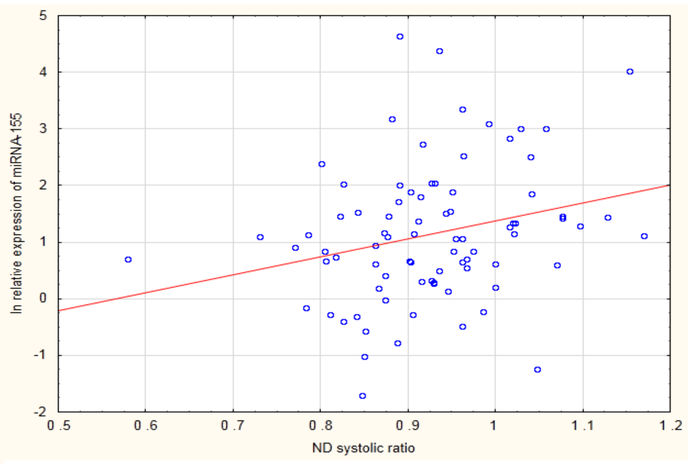

Fig. 5. Association between log relative expression of miR-155 and ND SBP, p = 0.05

Table 1. Baseline characteristics of the study group.

	Nocturnal normotension	Nocturnal hypertension	P value
Age (yr)	57 ± 15	62 ± 14	0.10
Plasma creatinine (mg/dl)	1.45 (1.1-1.95)	1.5 (1.1-2.1)	**0.004**
GFR (ml/min/1,73m2)	46 (30-60)	39 (23-59)	**0.004**
LDL (mg/dl)	99 ± 43	97 ± 34	0.85
HDL (mg/dl)	56 (41-68)	61 (47-76)	0.78
TG (mg/dl)	133 (109-177)	129 (80-183)	0.37
Total cholesterol (mg/dl)	183 ± 43	178 ± 38	0.63
C-reactive protein (mg/dl)	1.3 (0.61-2.3)	1.5 (0.7-4.6)	0.34
Hgb (g/dl)	13.7(13.1-14.6)	13.5 (12.3-14.5)	0.40
White blood cells (G/l)	7.68 (5.61-8.89)	7.19 (6.02 -8.48)	0.27
Neutrophils (G/l)	4.31 (3.30-5.23)	4.38 (3.73-5.95)	0.08
Lymphocytes (G/l)	1.98 (1.64-2.53)	1.73 (1.39 – 2.39)	0.44
Platelets (G/l)	233 (210-265)	205 (185-235)	**0.015**
Na (mmol/l)	141 (139-143)	141 (140-143)	0.87
BMI (kg/m^2)	25 (22-28)	28 (25-34)	**0.031**

GFR – glomerular filtration rate, LDL – low density lipoproteins, HDL – high-density lipoproteins, TG-triglicerides, CRP – C-reactive protein, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure

Plasma miR-155 expression maintained an independent association with night-day SBP (β = 0.24 p = 0.03) and average night-time SBP (β = 0.25 p = 0.02), at the multiple regression analysis adjusted for confounders (including CKD stage).

Conclusions

- MicroRNA-21 and microRNA-155 plasma expression is increased in patients with CKD and nocturnal hypertension.
- These miRNAs are upregulated in patients treated with alpha-blocker.
- According to microRNA gene target databases, both non-coding RNA particles regulate 3'UTR and promoter regions for genes involved in alpha adrenergic receptor signaling pathways.

References

1. Ghiadoni, L., S. Taddei, and A. Virdis, *Hypertension and endothelial dysfunction: therapeutic approach.* Curr Vasc Pharmacol, 2012. **10**(1): p. 42-60.
2. Grassi, G., et al., *Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives.* Hypertension, 2008. **52**(5): p. 925-31.
3. Okamoto, L.E., et al., *Nocturnal blood pressure dipping in the hypertension of autonomic failure.* Hypertension, 2009. **53**(2): p. 363-9.
4. Sachdeva, A. and A.B. Weder, *Nocturnal sodium excretion, blood pressure dipping, and sodium sensitivity.* Hypertension, 2006. **48**(4): p. 527-33.
5. Bankir, L., et al., *Nighttime blood pressure and nocturnal dipping are associated with daytime urinary sodium excretion in African subjects.* Hypertension, 2008. **51**(4): p. 891-8.
6. Lurbe, E., et al., *Added impact of obesity and insulin resistance in nocturnal blood pressure elevation in children and adolescents.* Hypertension, 2008. **51**(3): p. 635-41.
7. Higashi, Y., et al., *Circadian variation of blood pressure and endothelial function in patients with essential hypertension:a comparison of dippers and non-dippers.* J Am Coll Cardiol, 2002. **40**(11): p. 2039-43.
8. Vlachos, I.S., et al., *DIANA-TarBase v7.0: indexing more than half a million experimentally supported miRNA:mRNA interactions.* Nucleic Acids Res, 2015. **43**(Database issue): p. D153-9.
9. Kontaraki, J.E., et al., *Hypertrophic and antihypertrophic microRNA levels in peripheral blood mononuclear cells and their relationship to left ventricular hypertrophy in patients with essential hypertension.* J Am Soc Hypertens, 2015. **9**(10): p. 802-10.
10. Wang, L., et al., *Regulation of T lymphocyte activation by microRNA-21.* Mol Immunol, 2014. **59**(2): p. 163-71.

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