MUSCLE-RELATED miRNAS AND ITS RELATIONSHIP WITH CIRCULATING GDF15 AND FGF21 LEVELS IN PATIENTS WITH CARDIAC CACHEXIA

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INTRODUCTION

Cachexia is a multifactorial disorder, associated with several chronic disease, including Heart Failure (HF). Cardiac cachexia occurs with a prevalence up to 39% in patients with an advanced state of HF (NYHA, III and IV). This syndrome is the direct cause of death for more than 50% of patients with HF. Cachexia may be al least in part associated with muscle related miRNAs dysregulation.

AIM

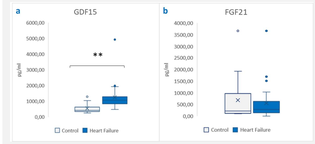
We aimed to identify specific muscle-related miRNAs profiling in plasma of patients with cardiac cachexia and novel serum biomarkers associated with this condition.

METHOD

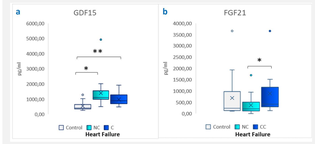
- We enrolled patients with Heart Failure (NYHA classes II-IV) and healthy subjects, serving as controls.
- Cardiac Cachexia was defined as involuntary weight loss > 6% in 6 months prior to enrollment.
- GDF15 and FGF21 serum levels were assessed by ELISA.
- Total RNA was extracted from plasma samples and circulating levels of miRNAs potentially involved in muscle wasting were analyzed by RT-PCR.

RESULTS

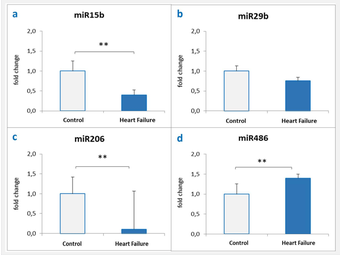
27 patients with **HF** and **17** healthy **controls** were enrolled (Table 1). Median **GDF15** serum levels were **higher in HF** patients vs controls (1065.60 vs 418.80, p<0.001), whereas median **FGF21** were **higher** in patients with **cardiac cachexia** vs those without cachexia (412.30 vs 201.60, p=0.046). Plasma **miR15b** median levels were **lower in HF** patients vs controls (0.80 vs 2.00, p= 0.002). In cachectic patients we found **lower** plasma levels of **miR29b** and **higher** of **miR486,** compared to controls (0.94 vs 1.60, p= 0.046 and 0.30 vs 0.20, p= 0.036, respectively). Moreover, circulating **miR15b** showed a **negative correlation** with **GDF15** serum levels (R= -0.33; p= 0.029) (see Figures).



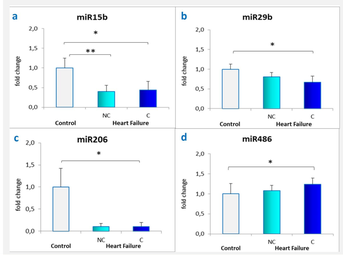
Serum levels (pg/ml) of GDF15 (a) and FGF21 (b) in HF patients and controls.
*** p <0.02*



Serum levels (pg/ml) of GDF15 (a) and FGF21 (b) in Cachectic and not cachectic HF patients and controls.
*** p <0.02*
** p <0.05*



Expression levels of miRNAs involved in muscle wasting evaluated in plasma samples of HF patients and controls.
*** p <0.02.*
All results were standardized with miRNAs expression level of control group = 1.0



Expression levels of miRNAs involved in muscle wasting in Cachectic (C), not cachectic (NC) HF patients and control group.
*** p <0.02.*
** p <0.05*
All results were standardized with miRNAs expression level of control group = 1.0

Participants *N*= 44	Cachectic patients *N*= 10	Non-Cachectic patients *N*= 17	Controls *N*= 17	p value*
Male/Female	6/4	4/13	6/10	p= 0.165
Age (y)	77.60 ± 6.85	79.82 ± 7.45	57.65 ± 11.08	p= 0.446
BMI, (kg/ m²)	23.70 ± 4.13	25.71 ± 3.45	25.02 (23.87; 26.86)	p= 0.484
Weight loss (% in 6 months)	7.47 (6.38; 11.65)	0.00 (0.00; 0.98)	0.00 (0.00; 0.00)	p < 0.001
CRP, mg/dl	2.69 (1.56; 8.57)	1.06 (0.13; 2.37)	-	p= 0.030
Albumin, g/dl	3.50 (3.2; 3.75)	3.80 (3.20; 4.00)	-	p= 0.182
Creatinin, mg/dl	0.99 (0.86; 1.75)	0.93 (0.73; 1.24)	-	p= 0.386
Hemoglobin, g/dl	11.28 ± 1.65	11.35 ± 1.57	-	p= 0.911
LVMI, g/ m² Male LVMI, g/m² Female	145.50 ± 31.48 192.67 ± 36.61	188.67± 50.21 141.88 ± 39.11	101.80 ± 11.58 86.67 ± 10.21	p= 0.548 p= 0.258

Table 1. *Characteristics of participants. Patients with HF were subdivided by the presence of cardiac cachexia (weight loss > 6%). Data are shown as Mean ± SD, or as Median (interquartile range). Abbreviations: BMI, Body Mass Index; CRP, C-Reactive Protein; LVMI, Left-Ventricular Mass Index. *Cachectic vs Non-Cachectic patients.*

CONCLUSIONS

- ✓ **GDF15** levels were modulated in HF
- ✓ **FGF21** were increased in patients with cardiac cachexia.
- ✓ **miR29b** and **miR486** seem to play a key role in cardiac cachexia.
- ✓ **miR15b** was downregulated in HF and negatively correlated with GDF15 levels.

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