STUDY OF THE CONTRIBUTION OF MODULATORS OF IRON HOMEOSTASIS IN HEART FAILURE

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Introduction: Heart failure (HF) is considered one of the biggest public health problems, affecting 2% of the world's population. Is defined as a clinical syndrome due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise. It can be influenced by several genetic modulators, in particular genes responsible for the balance of iron metabolism, such as the *HFE*, *SLC40A1* and *TMPRSS6* genes.

Aims: Investigate the contribution of common genetic variants in *HFE* (C282Y - rs1800562 and H63D - rs1799945), *SLC40A1* (rs1439816 and rs2304704) and *TMPRSS6* (rs855791) to HF, as well as to understand the effect of various biochemical parameters, such as serum iron, ferritin, hemoglobin (Hb), Mean Globular Volume (VGM), Red Cell Distribution Width (RDW) and Total Iron-Binding Capacity (TIBC).

Materials and Methods: The study included a population of 301 HF patients and 361 controls. Patients were also categorized into those with HF in the form of preserved ejection fraction (HFpEF) or non-preserved ejection fraction (HFnpEF). The polymorphic analysis of the *HFE* gene variants (C282Y and H63D) was realized using the Multiplex PCR-ARMS technique, while the Endpoint Genotyping PCR technique was used for the remaining variants. Statistical analysis was done using SPSS software, version 28.0, with a statistical significance level of $p<0.05$.

Results:

Biochemical Parameters	HF			HFpEF			HFnpEF			Reference values
	Mean (min. – max.)			Mean (min. – max.)			Mean (min. – max.)			
	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value	
Serum iron	41.400[a] (12.9 - 248.0)	39.300[a] (7.5 – 176.0)	0.359	40.350[a] (12.9 – 145.8)	39.300[a] (13.1 – 144.0)	0.997	44.050[a] (17.7 – 248.0)	39.300[a] (7.5 – 176.0)	0.145	Men: 75 - 175 µg/dL Women: 65 - 165 µg/dL
Ferritin	130.600[a] (18.4 - 1940.0)	233.000[a] (8.4 – 1116.6)	**0.035**	133.800[a] (18.4 – 1940.0)	315.900[a] (33.8 – 1116.6)	**0.011**	164.500[a] (32.1 – 1139.0)	159.350[a] (8.4 – 814.0)	0.883	Men: 15 - 300ug/l Women: 15 - 200ug/l
Hb	11.549[b] (7.1 - 17.1)	11.781[b] (6.4 – 17.9)	0.466	11.342[b] (7.1 – 17.1)	11.408[b] (7.6 – 17.9)	0.890	11.817[b] (8.4 – 15.4)	12.060[b] (6.4 – 16.9)	0.579	12.0 – 16.5g/dL
VGM	88.550[a] (62.9 - 104.0)	91.250[a] (73.9 – 107.8)	**0.005**	88.562[b] (62.9 – 104.0)	93.269[b] (73.9 – 107.8)	**0.004**	88.611[b] (70.4 – 99.9)	89.635[b] (74.2 – 106.8)	0.481	103.2 – 126.3fL
RDW	15.300[a] (12.8 - 24.2)	15.500[a] (12.8 – 26.0)	0.515	15.300[a] (13.2 – 24.2)	15.000[a] (12.8 – 20.1)	0.599	15.400[a] (12.8 – 19.0)	15.600[a] (13.0 – 26.0)	0.349	11% - 14%
TIBC	284.48[b] (92.0 - 476.0)	270.98[b] (137.0 – 483.0)	0.383	286.75[b] (168.0 – 428.0)	253.91[b] (144.0 – 434.0)	0.116	277.0[b] (92.0 – 476.0)	286.68[b] (137.0 – 483.0)	0.696	250 - 450ug/l

[a] – Median value; [b] - Media value

Serum Iron

Gene	Genotypes	HF					
		Women			Men		
		N (%)	Mean of serum iron (µg/dL)[a]	p-value[1]	N (%)	Mean of serum iron (µg/dL)[a]	p-value[1]
***HFE* – H63D (rs1799945)**	**DD/HD**	46 (73.0%)	48.500	**0.006**	27 (57.4%)	40.000	0.962
	HH	47 (57.3%)	35.400		43 (55.1%)	37.100	
***SLC40A1* (rs1439816)**	**CC/CG**	32 (69.6%)	46.250	0.212	26 (74.3%)	44.600	**0.035**
	GG	67 (71.3%)	37.200		52 (65.8%)	33.400	
***TMPRSS6* (rs855791)**	**AA/AG**	62 (68.9%)	37.050	0.243	49 (67.1%)	33.100	**0.018**
	GG	34 (68.0%)	46.500		28 (70.0%)	47.900	

[1] – Mann Whitney U-Test; [a] – Median value; [b] – Media value

Gene	Genotypes	HFpEF					
		Women			Men		
		N (%)	Mean of serum iron (µg/dL)[a]	p-value[1]	N (%)	Mean of serum iron (µg/dL)[a]	p-value[1]
***SLC40A1* (rs1439816)**	**CC/CG**	17 (89.5%)	48.100	0.184	11 (91.7%)	63.100	**0.036**
	GG	39 (86.7%)	35.400		22 (84.6%)	32.250	

[1] – Mann Whitney U-Test; [a] – Median value; [b] – Media value

Gene	Genotypes	HFnpEF					
		Women			Men		
		N (%)	Mean of serum iron (µg/dL)[a]	p-value[1]	N (%)	Mean of serum iron (µg/dL)	p-value[1]
***HFE* – H63D (rs1799945)**	**DD/HD**	12 (75.0%)	52.500	**0.02**	13 (50.0%)	47.200[a]	0.276
	HH	16 (39.0%)	36.000		27 (47.4%)	33.700[a]	

[1] – Mann Whitney U-Test; [a] – Median value; [b] – Media value

Ferritin

Gene	Genotypes	HF					
		Women			Men		
		N (%)	Mean of ferritin (µg/L)[a]	p-value[1]	N (%)	Mean of ferritin (µg/L)[a]	p-value[1]
***SLC40A1* (rs2304704)**	**GG/GA**	81 (66.4%)	141.000	**0.003**	63 (70.8%)	186.000	0.136
	AA	15 (75.0%)	58.900		14 (58.3%)	353.450	

[1] – Mann Whitney U-Test; [a] – Median value; [b] – Media value

VGM

Gene	Genotypes	HF					
		Women			Men		
		N (%)	Mean of VGM (fL)	p-value	N (%)	Mean of VGM (fL)[a]	p-value[1]
***SLC40A1* (rs2304704)**	**GG/GA**	92 (75.4%)	89.050[b]	**0.012**[2]	68 (76.4%)	90.543	0.101
	AA	16 (80.0%)	84.150[b]		15 (62.5%)	94.060	

[1] – Levene Test; [2] – Mann Whitney U-Test; [a] – Media value; [b] – Median value

Gene	Genotypes	HFpEF					
		Women			Men		
		N (%)	Mean of VGM (fL)	p-value	N (%)	Mean of VGM (fL) [a]	p-value[1]
***SLC40A1* (rs2304704)**	**GG/GA**	54 (93.1%)	89.750[b]	**<0.001**[2]	27 (96.4%%)	92.933	0.640
	AA	6 (100.0%)	81.650[b]		9 (90.0%)	94.278	

[1] – Levene Test; [2] – Mann Whitney U-Test; [a] – Media value; [b] – Median value

Conclusion:

In general, the biochemical parameters indicate ferropenic anemia. We can find more differences between the sexes in HFpEF. All the genes are modulating the biochemical parameters, but *SLC40A1* has the greatest genetic contribution. Women are more susceptible to genetic modulation. To increase knowledge on the subject, other genes and other parameters that seem to influence the disease could be studied.

References:

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