METABOLOMIC APPROACH TO WHITE MATTER LESIONS IN CHRONIC HEMODIALYSIS PATIENTS IDENTIFIES A NOVEL METABOLIC PROFILE ASSOCIATED WITH THESE LESIONS

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CONTEXT AND OBJECTIVES

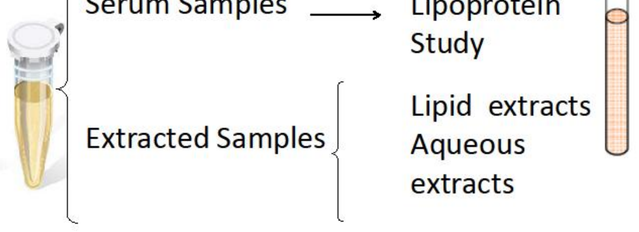
Nearly half of chronic hemodialysis (HD) patients have **white matter lesions** (WML_s), a form of small-vessel cerebrovascular disease[1].

Whereas advanced age and hypertension are the most accepted risk factors for these lesions, the role of other factors such as plasma lipids is controversial.

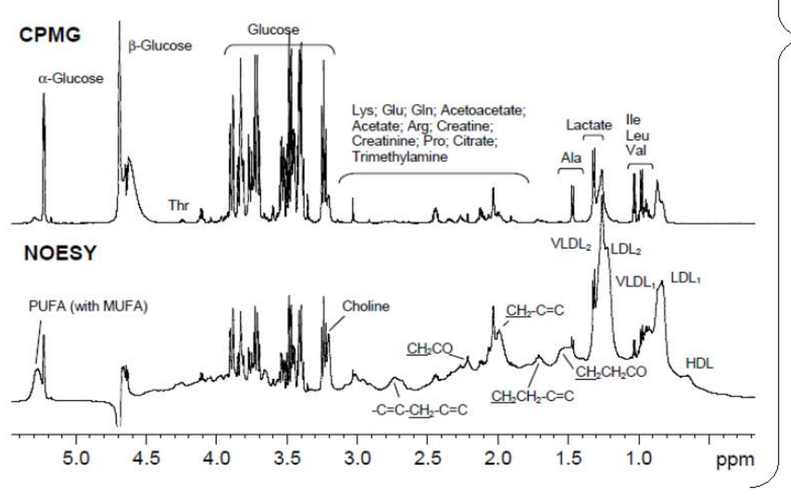
The aim of this study is **to identify a plasmatic metabolic profile** associated with these lesions by ^{1}H- Nuclear magnetic resonance(NMR) based-on metabolomics.

MATERIALS AND METHODS

A cohort of **63 chronic HD patients** were classified into two groups depending on the presence (n=34) or absence (n=29) of WML_s



NMR analysis



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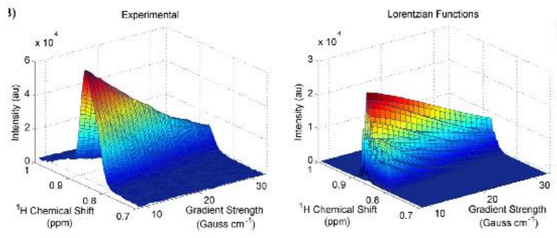
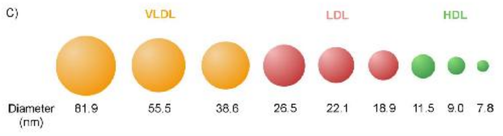


TEST LIPOSCALE for Lipoprotein Profiling[2]



Univariate & Multivariate statistical analysis

- Wilcoxon Rank sum test
- Partial Least-Squares Discriminant Analysis (PLS-DA)
- Receiving Operating characteristic (ROC) classifier

RESULTS

- PLS-DA of the NMR and clinical data showed a noticeable separation into the two groups. The classification capability of the cross-validated PLS-DA (Figure 1 and Figure 2) remained significant after permutation testing (p<0.0001).

Figure 1. Receiving Operating characteristic (ROC) curve.

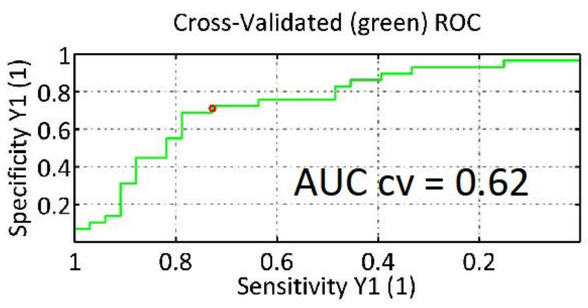


Figure 2. PLS-DA model to distinguish WMLs groups.

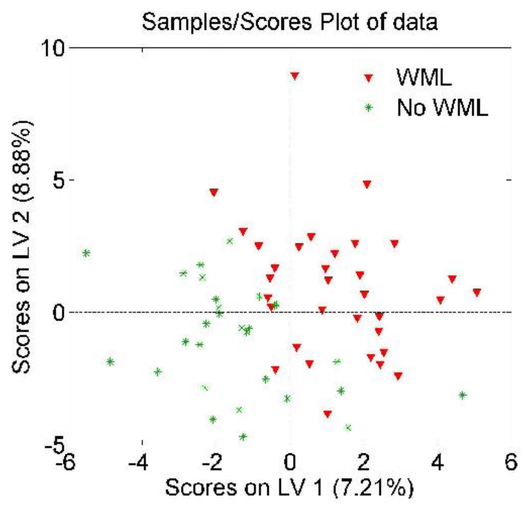
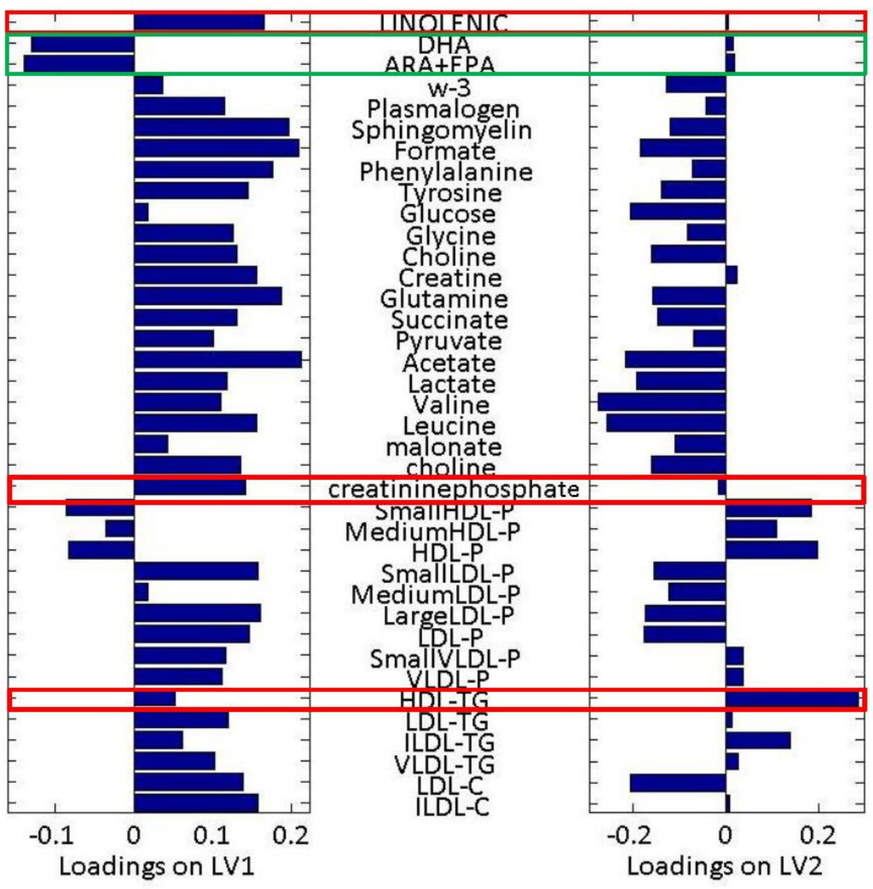


Figure 3. Contribution of the variables on the PLS-DA model.



- A pro-atherogenic metabolic profile was related to WML_s, presenting a tendency to increased VLDL related variables (LV1 > 0), triglyceride related variables, LDL-C, VLDL-C (LV1 > 0) and, remarkably, HDL-triglycerides (LV1 and LV2 >0) (Figure 3, Table 1).
- Patients without WML_s presented a protective pattern against developing atherosclerosis characterized by increased levels eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids (LV1 < 0, Figure 3).
- The pro-atherogenic pattern was positively associated with the inflammatory and oxidative stress markers, including plasma glutathione, CRP_{us} and IL-6, only in the WML_s group.
- Linoleic acid was 30% increased in the WML_s group (p = 0.048) as well as Creatinine Phosphate (7% increased, p = 0.018).

Table 1. Lipoprotein Profile, Univariate statistical analysis

Variable	Units	CKD (No-WML) Median ± IQR	CKD (WML) Median ± IQR	p NoWML/ WML
VLDL-C	mg/dl	19.6 ±22.8	26.1 ±24.5	0.3
IDL-C	mg/dl	9.33 ±5.37	9.63 ±9.43	0.45
LDL-C	mg/dl	82.3 ±81.1	105 ±67	0.5
HDL-C	mg/dl	28.9 ±24.2	24.5 ±18.5	0.47
VLDL-TG	mg/dl	89.8 ±99.2	118 ±98	0.49
IDL-TG	mg/dl	8.58 ±3.99	8.08 ±5.39	0.71
LDL-TG	mg/dl	17.5 ±13.3	22.7 ±10.1	0.22
HDL-TG	mg/dl	13.0 ±5.5	15.9 ±6.5	**0.026**
VLDL-P	nm/L	62.9 ±70.6	87.5 ±71.1	0.39
L- VLDL	nm/L	1.71 ±1.60	1.83 ±1.65	0.67
M- VLDL	nm/L	8.94 ±11.6	11.6 ±10.4	0.48
S-VLDL	nm/L	52.8 ±56.9	73.4 ±59.7	0.37
LDL-P	nm/L	629 ±586	832 ±477	0.38
L-LDL	nm/L	100 ±95	144 ±94	0.31
M- LDL	nm/L	179 ±140	205 ±132	0.93
S-LDL	nm/L	345 ±317	485 ±344	0.32
HDL-P	µm/L	17.8 ±9.4	18 ±8.5	0.74
L-HDL	µm/L	0.18 ±0.11	0.22 ±0.11	0.1
M HDL	µm/L	4.4 ±5.76	5.67 ±2.78	0.44
S-HDL	µm/L	10.8 ±5.7	11.4 ±8.4	0.67
VLDL-Z	Ø (nm)	42.2 ±0.4	42.2 ±0.4	0.37
LDL-Z	Ø (nm)	21 ±0.32	21.02 ±0.2	0.64
HDL-Z	Ø (nm)	8.2 ±0.16	8.26 ±0.22	0.29

CONCLUSIONS

Triglycerides-enrichment of HDL and elevated inflammatory parameters, increased in chronic HD patients with WMLs, are known to impair reverse cholesterol transport, and might be linked with small-vessel disease by a diminished cholesterol efflux capacity in the sub-endothelial space of cerebral microvessels.

Abbreviations:
VLDL related variables: VLDL-C: VLDL cholesterol; VLDL-TG: VLDL triglycerides VLDL-P: Total VLDL Particle concentration; L-VLDL, M-VLDL and S-VLDL : Large, Medium and Small VLDL Particle concentration; VLDL-Z: VLDL Size.
LDL related variables: LDL-C: LDL cholesterol; LDL-TG: LDL triglycerides. LDL-P: Total LDL Particle concentration; L-LDL, M-LDL and S-LDL : Large, Medium and Small LDL Particle concentration; LDL-Z: LDL Size.
HDL related variables: HDL-C: HDL cholesterol; HDL-TG: HDL triglycerides. HDL-P: Total HDL Particle concentration; L-HDL, M-HDL and S-HDL : Large, Medium and Small HDL Particle concentration; HDL-Z: HDL Size.

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