Application of metabolomics to the evaluation of kidney function and kidney transplantation

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Introduction

Chronic kidney disease (CKD), is a common disease that affects 5 to 10% of the general population(1). When its most severe form called end-stage renal disease (ESRD) occurs, kidney transplantation (KTx) is regarded as the most favorable approach in terms of quality of life, morbidity and mortality(2). However, KTx is not devoid of risks and the follow-up of kidney graft function is crucial in the management of kidney transplantation recipients (KTRs) (3)(4). Today, routine techniques for monitoring renal function are based on serum creatinine that remains rather imprecise to accurately reflect the renal function which is classically estimated (eGFR). GFR (Glomerular Filtration Rate) can be precisely measured but its measurement is time-consuming and therefore rarely performed in clinical routine. Because of these limits the need of new biomarkers able to precisely estimate the renal function or even predict its evolution in KTRs patients is a key challenge to improve patients' management.

In this project, by a NMR-based metabolomics approach we plan to identify several metabolites or a metabolomic pattern that could be correlated to kidney function evolution by studying urine samples coming from French KTRs. Moreover, we aim also to improve our knowledge of the metabolome that could be linked to a GFR decrease and by combining clinical and metabolomics data to obtain a model that could predict the kidney function issue.

Clinical side

82 KTRs recruited at Bichat-Claude-Bernard Hospital in Paris

Kidney transplantation

Urine collection and clinical parameters' measurement

3months post-KTx

Patients stratification

GFR measured

3 months	12 months
EDTAP deindex	EDTAP deindex
52.31092804	56.34950848
74.45472067	61.16890504
99.07687909	69.15452995
74.75974699	75.05988531
66.93178632	50.0903414
72.70050047	39.0094855
58.28078498	70.72727786
34.1453532	71.47958469
46.21995132	61.24211609
61.0867325	35.42987839
40.7831434	48.49158358
41.62095034	61.21524373
59.96432951	43.69739866
62.16305442	47.29876994

$$\% \text{ renal function} = \frac{(12m\ GFR - 3m\ GFR)}{3m\ GFR} * 100$$

Classified in

Decrease = renal function is between -7% and -47%

Stable = renal function is between -6% and +47%

Urine collection and clinical parameters' measurement

12months post-KTx

Metabolomics

Workflow

3months urine sample

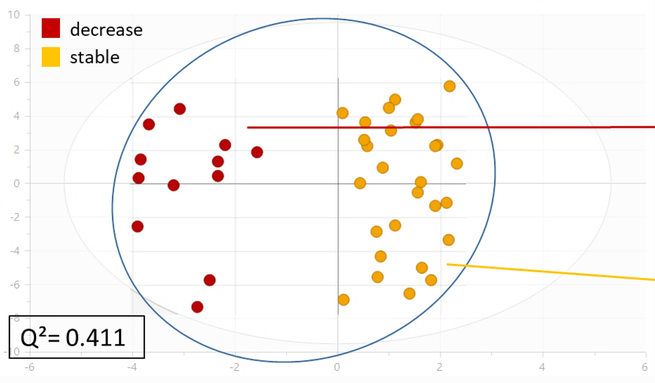
^{1}H-NMR
NOESY-presat sequence

Spectra processing

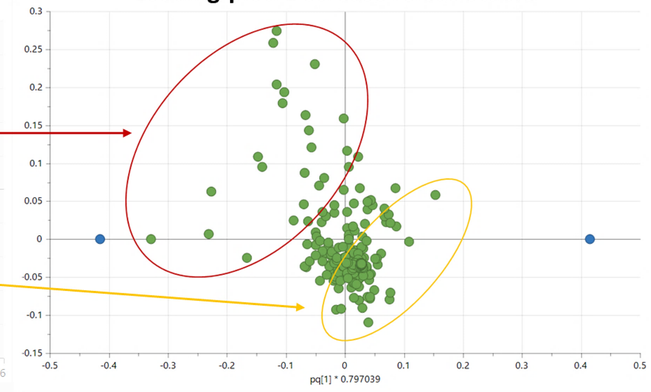
Datamatrix for statistical analysis

Statistical analysis

OPLS-DA model : Decrease *versus* Stable



Loading-plot: Decrease *versus* Stable



Multivariate analysis: Orthogonal Projections to Latent Structures Discriminant Analysis (OPLS-DA) of urine samples showing a separation between decrease versus stable GFR (Q^2= 0.411). The features responsive for the separation were identified by a loading–plot and a panel of predictive biomarkers was settle.

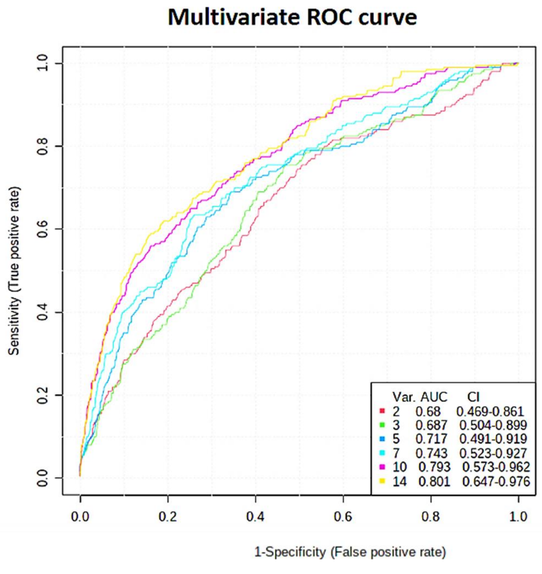
Patients' status prediction: conclusion and prospective

The value of buckets was used for univariate analysis

Mann-Whitney t-test was applied (p-value< 0.05)

14 significant metabolites up- and down-regulated were found and used for build a multivariate ROC curve

Multivariate ROC curve



Mann–Whitney test was used for underline significant features for comparisons between two groups. By a multivariate receiver operating characteristic curve (ROC curve), the diagnostic ability of our model was tested showing how the best model is obtained by considering 14 features (AUC= 0.801).

In conclusion these preliminary results suggest that the GFR evolution at 12 months can be predict by measuring the urinary levels of selected metabolites at 3 months post KTx.

Based on these promising first results, we aim to increase our metabolites exploration by applying a MS metabolomics approach to the cohort. The combination of the different analytical and clinical datasets will probably help us to improve our model and to extract common traits that will constitute key elements in the perspective of a more comprehensive vision of the biochemical events that occur during the Kidney function degradation.

Reference

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