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Article

Uremic Toxins and Inflammation: Metabolic Pathways Affected in Patients Undergoing Renal Replacement Therapies

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Abstract: 3.9 million individuals rely on kidney replacement therapy worldwide. They experience heightened susceptibility to cardiovascular diseases and mortality, alongside an increased risk of infections and malignancies, with inflammation being key to explaining this intensified risk. This study utilized semi-targeted metabolomics to explore novel metabolic pathways related to inflammation in this populations. We collected pre and post-session blood samples of patients who had already undergone one year of chronic hemodialysis. And used liquid chromatography and high resolution mass spectrometry to perform a metabolomic analysis. Afterwards, we employed both univariate (Mann-Whitney test) and multivariate (logistic regression with LASSO regularization) to identify metabolites associated with inflammation. In the univariate analysis, in-dole-3-acetaldehyde, 2-ketobutyric acid, and urocanic acid showed statistically significant decreases in median concentrations in the presence of inflammation. In the multivariate analysis, metabolites positively associated with inflammation include allantoin, taurodeoxycholic acid, norepinephrine, pyroglutamic acid, and L-hydroxyproline. Conversely, metabolites showing negative associations with inflammation include benzoic acid, indole-3-acetaldehyde, methionine, citrulline, alphaketoglutarate, n-acetyl-ornithine and 3,4-dihydroxybenzeneacetic acid. Non inflamed patients exhibit preserved autophagy and reduced mitochondrial dysfunction. Understanding inflammation in this group hinges on the metabolism of arginine and the urea cycle. Additionally, the microbiota, particularly uricase-producing bacteria and those metabolizing tryptophan, play critical roles.

Keywords: uremic toxins and inflammation; metabolic pathways affected in patients undergoing renal replacement therapies

1. Introduction

Chronic kidney disease (CKD) is an escalating global health threat with an estimated 850 million individuals living with the disease in 2017 and it being the third fastest-growing cause of death [1]. Of those individuals, approximately 3.9 million globally rely on kidney replacement therapy (KRT) indefinitely [1], predominantly through hemodialysis. They face an elevated risk of cardiovascular illness and death and are more prone to infections and malignancies [2]. For instance, in the age group of 40-44 years, there is a notable gap in life expectancy between men undergoing dialysis (10.9 years) and men in the general population (36.5 years), exceeding 25 years (over 30 years for women) [1]. Cardiovascular disease (CVD) impacts over two-thirds of individuals undergoing hemodialysis, representing a significant source of morbidity and contributing to nearly half of all mortality cases [3].



Inflammation serves as a crucial link between chronic kidney disease and cardiovascular issues and is related to the prognosis of this group of patients. For example, inflammation directly results in hemodynamic strain, elevating ventricular wall pressure, initiating myocardial stun, and prolonged exposure ultimately culminates in irreversible myocardial injury [4]. Inflammation in end-stage renal disease (ESRD) patients undergoing KRT arises from various factors such as the exposure to the dialysis membranes, the presence of central venous catheters, sodium and water overload, internal dysbiosis which may lead to uremic toxins accumulations and oxidative stress mediated by mitochondrial dysfunction and cellular senescence [5]. In connection with this, while some medium-sized molecule toxins have been identified as pivotal in this pathology, there are still numerous metabolic pathways yet to be explored [6].

To do this, metabolomics emerges as a promising avenue for unraveling novel pathways within the broader field of 'omics' sciences. This discipline employs diverse analytical techniques to identify and quantify small molecules (metabolites) in biological samples, offering insights to the individual phenotype as it accounts for both the genome and the extrinsic factors such as lifestyle, medications and underlying health conditions. This makes it a particularly suitable tool to assess uremic toxins in the body.

Untargeted metabolomics, which focuses on the comprehensive detection and relative quantification of metabolites, but can make the exact identification of metabolites difficult, has been utilized to investigate the changes in the metabolic profile in hemodialysis patients before and after sessions and comparing different hemodialysis techniques [7–9]. Meanwhile, targeted metabolomics, which is used to perform a precise measurement of predefined, much smaller groups of metabolites, has been employed to evaluate alterations in endocannabinoid and oxylipin levels among haemodialysis patients, correlating these changes to inflammatory processes [10].

However, in the present work we decided to employ semitargeted metabolomics to examine the potential biological signature for inflammation in patients who have undergone one year of chronic hemodialysis.

We use an in-house polar compound library to facilitate the identification of measured metabolites within a unified workflow which serves as a bridge between untargeted and targeted procedures. This allows us to broaden the search scope for potential metabolites related to inflammation while accurately identifying them.

In this way, we aim to characterize the metabolic profile within this cohort, with a particular emphasis on inflammation-associated metabolites as potential therapeutic target.

2. Results

The study group, with an average age of 68.97 years ($SD \pm 14.18$), comprised 37% females and showed an average height of 165.23 cm ($SD \pm 8.87$) and a mean weight of 75.03 kg ($SD \pm 16.73$). Approximately 54% of the patients were smokers, and an equivalent percentage had type 2 diabetes. Hypertension was prevalent in 93% of the cohort, while dyslipidemia was present in 79%.

The summary of the demographic and clinical characteristics of the sample (n=43) can be found in Table 1.

Table 1. Demographic characteristics of the sample.

Variable	Mean/frequency
Age (years) (mean \pm SD)	68.97 \pm 14.18
Female gender, n (%)	16 (37%)
Height (cm) (mean \pm SD)	165.23 \pm 8.87
Weight (kg) (mean \pm SD)	75.03 \pm 16.73
BMI (mean \pm SD)	27.75 \pm 4.76
Smoker, n (%)	23 (53,5%)
Type 2 diabetes, n (%)	21 (48,8%)
Hypertension, n (%)	40 (93%)

Dyslipidemia, n (%)	34 (79.1%)
Urea (mg/dl) (mean \pm SD)	88.70 \pm 25.59
Uric acid (mg/dl) (mean \pm SD)	4.97 \pm 1.22
Corrected calcium for serum albumin (mg/dl) (mean \pm SD)	9.13 \pm 0.77
Phosphate (mg/dl) (mean \pm SD)	4.26 \pm 1.13
Sodium (mEq/L) (mean \pm SD)	139.84 \pm 2.98
Potassium (mEq/L) (mean \pm SD)	4.70 \pm 0.69
Chloride (mEq/L) (mean \pm SD)	106 \pm 4.33
CRP (mg/L) (mean \pm SD)	14.24 \pm 57.29
Hemoglobin (g/dl) (mean \pm SD)	9.5 \pm 1.35
Leukocytes ($\times 10^9$ /L) (mean \pm SD)	7.03 \pm 2.30
Platelets ($\times 10^9$ /L) (mean \pm SD)	198.53 \pm 62.55
AVF as a venous access, n (%)	24 (55.8%)
Hemodiafiltration as KRT, n (%)	32 (74.4%)
Average interdialysis weight gain (cc) (mean \pm SD)	1622.5 \pm 1018.67
Kt/V (mean \pm SD)	1.7 \pm 0.5
Residual diuresis (cc) (mean \pm SD)	2097.67 \pm 765.08
Inflamed patients defined as CRP \geq 2 mg/L, n (%)	23 (67%)

A semi-targeted metabolic strategy was utilized, employing liquid chromatography and high-resolution mass spectrometry alongside an in-house library of polar compounds. The found metabolites and their mass to charge ratios are available in the supplementary material. Both univariate (Mann-Whitney test) and multivariate (logistic regression with LASSO (Least Absolute Shrinkage and Selection Operator) regularization) analyses were conducted to identify metabolomic variables linked to inflammation.

The analyzed patients had already undergone one year of hemodialysis, and we obtained samples before and after a session to try to identify which metabolites change with the procedure.

A numerical summary of the pre-session samples is provided the Table 2, including the respective medians and interquartile ranges of the variables with significant changes between the two groups, and Figure 1 visually represents this information in a volcano plot.

In the pre-session samples, the median concentrations of indole-3-acetaldehyde ($p=0.0023$), 2-ketobutyric acid ($p=0.0196$), and urocanic acid ($p=0.0323$) significantly decreased in the presence of inflammation, as indicated by a statistically significant Mann-Whitney test. The magnitude of change was greater in carnitine, which saw a decrease in median concentration by a factor of 1.39 in inflamed patients, and lowest in trehalose, with a decrease by only a 0.75-factor.

Table 2. Numerical summary of metabolomic variables with significant differences in their medians based on inflammation=no and inflammation=yes.

Variable	Median inflammation =No	IQR inflammation =No	Median inflammation =Yes	IQR inflammation =Yes	Mann- Whitney statistic	p-value
Indole-3-acetaldehyde	1190130	579521	778141	467437	316	0.0023
tryptophan	2988287	2263933	2191984	1182744	313	0.0031
methionine	937980	238906	641991	319903	310	0.0041
Benzoic acid	42742	18539	29556	14609	309	0.0045
carnitine	82227848	73058260	58997524	53464650	295	0.0145
2-Ketobutyric acid	872432	494891	517984	433389	291	0.0196
alanine	7982122	1829652	6727464	1840257	286	0.0281
Urocanic acid	15909	15612	8828	13043	284	0.0323

2-Methyl-3-ketovaleric acid	65164816	25911640	51769852	22772580	284	0.0323
trehalose	74993	45349	100659	51935	123	0.0370
D-2-Aminobutyric acid	467418	132337	379133	248834	282	0.0370
N-Acetyl-L-phenylalanine	50225	36626	70619	56563	124	0.0396
tyrosine	2760424	852724	2470091	1027556	280	0.0423
N-Acetylcarnitine	31762998	18670840	26701374	14508230	278	0.0481

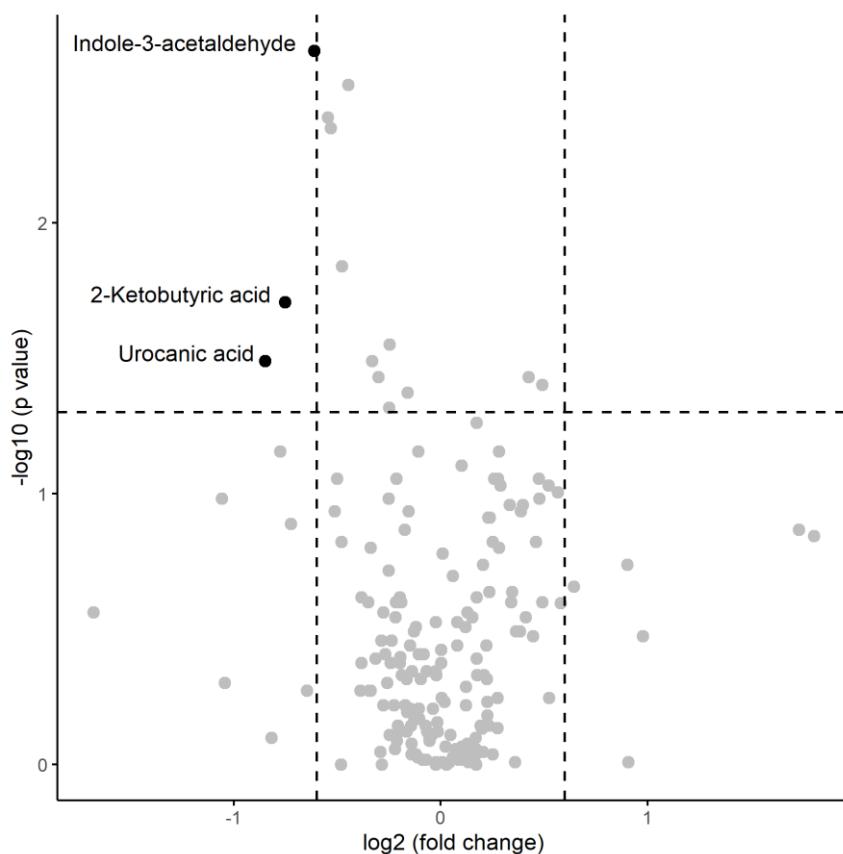


Figure 1. Volcano plot of metabolomic variables. The horizontal dashed line represents the limit of statistical significance (corresponding to p -value = 0.05); values above it denote variables with significantly different medians. The vertical dashed lines represent a $\log_2(\text{foldchange})$ of -0.6 and +0.6. Values above + 0.6 represent variables with a median for inflammation=yes that is 1.5 times in greater magnitude than for inflammation=no. Values below -0.6 represent variables with a median for inflammation=no that is 1.5 times greater in magnitude than for inflammation=yes.

Table 3 reports the standardized coefficients (SC) and odds-ratio (OR) associated with each metabolite and Figure 2 visually represents the OR obtained in the logistic-LASSO model.

Regarding this multivariate analysis, metabolites showing positive associations with inflammation (inflammation=yes) include allantoin (SC=1.17, OR 3.22), taurodeoxycholic acid (SC=0.43, OR=1.54), norepinephrine (SC=0.4, OR 1.49), pyroglutamic acid (SC=0.38, OR=1.46), and L-hydroxyrootic acid (SC=0.29, OR=1.34), whereas benzoic acid (SC=-0.97, OR 0.38), indole-3-acetaldehyde (SC=-0.74, OR 0.48), methionine (SC=-0.71, OR 0.49), citrulline (SC=-0.60, OR 0.55), alpha-ketoglutarate (SC=-0.55, OR=0.55), n-acetyl-l-ornithine (SC=-0.53, OR 0.59), and 3,4-dihydroxybenzeneacetic acid (SC=-0.40, OR 0.67) show negative associations. Additionally, n-

acetylcarnitine (SC=-0.17, OR 0.85), 3-indolepropionic acid (SC=-0.17, OR 0.85), pantothenate (SC=-0.16, OR 0.85), and cholic acid (SC=-0.15, OR 0.86) exhibit minor negative influences. Odds ratios close to 1 indicate variables with a lesser impact on the model.

Table 3. Variables, standardized coefficients, and Odds Ratios obtained (LASSO).

Variables	Coef.estandarizados	Odds Ratio
<i>Allantoin</i>	1.1695281	3.2204726
<i>Benzoic acid</i>	-0.9747088	0.3773022
<i>Indole-3-acetaldehyde</i>	-0.7354908	0.4792702
<i>methionine</i>	-0.7067793	0.4932302
<i>Citrulline</i>	-0.5962893	0.5508519
<i>α-ketoglutarate</i>	-0.5466127	0.5789074
<i>N-acetyl-L-ornithine</i>	-0.5330003	0.5868416
<i>Taurodeoxycholic acid</i>	0.4326940	1.5414044
<i>3-4-Dihydroxybenzeneacetic acid</i>	-0.4005447	0.6699550
<i>Norepinephrine</i>	0.4000314	1.4918716
<i>Pyroglutamic acid</i>	0.3795375	1.4616085
<i>L-Hydroorotic acid</i>	0.2959347	1.3443824
<i>N-Acetylcarnitine</i>	-0.1682766	0.8451200
<i>3-Indolepropionic acid</i>	-0.1674606	0.8458099
<i>pantothenate</i>	-0.1585006	0.8534225
<i>Cholic acid</i>	-0.1503721	0.8603877
<i>Guaiacol</i>	0.1375204	1.1474251
<i>4-Pyridoxic acid</i>	-0.1233154	0.8839848
<i>b-Aminoisobutyric acid</i>	0.1005446	1.1057730
<i>3-Methyl-Histidine</i>	0.0429894	1.0439269
<i>O-phosphohomoserine</i>	0.0415483	1.0424235
<i>Ureidosuccinic acid</i>	0.0387375	1.0394976
<i>creatine</i>	-0.0143093	0.9857926
<i>xanthosine</i>	0.0020708	1.0020730

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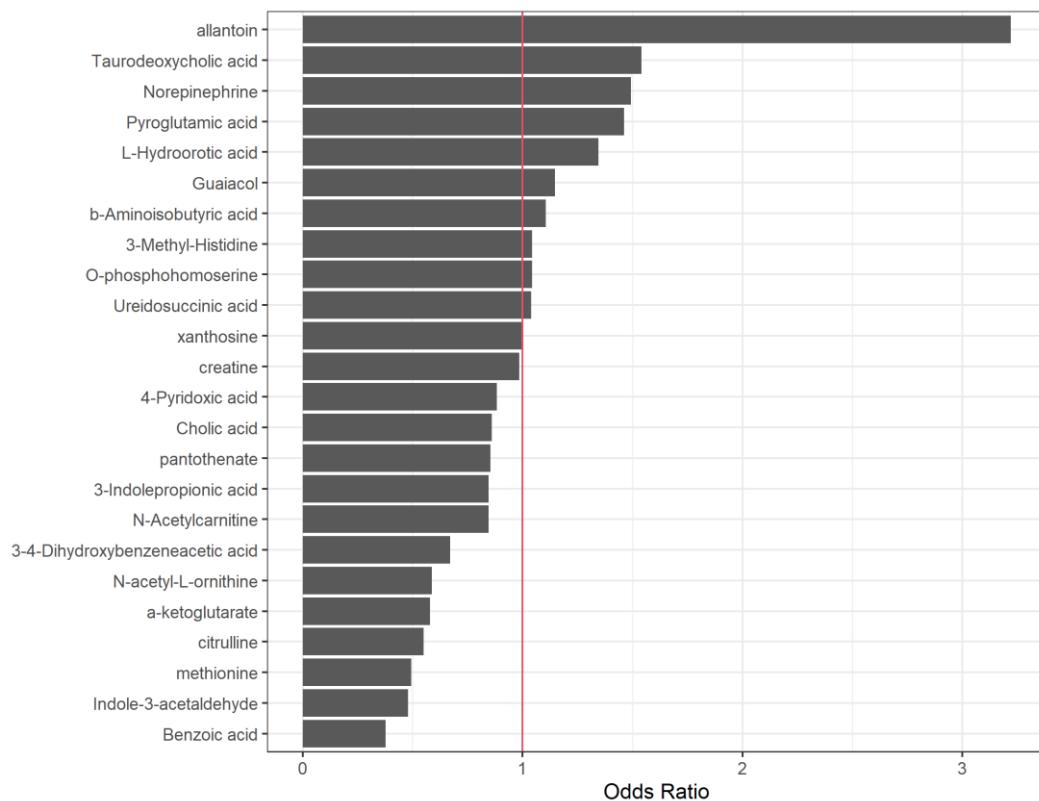


Figure 2. Graphical depiction of the OR obtained in the Logistic-LASSO model. ORs close to 1 (red vertical line) indicate variables with lesser impact on the model.

A numerical summary of the results obtained in the post-session samples is provided the Table 4, including the respective medians and interquartile ranges of the variables showing significant changes between the two groups, and Figure 3 visually represents this information in a volcano plot.

Regarding this, univariate analysis revealed significant variables that also exhibited a substantial change in the magnitude of their medians: m-coumaric acid showed higher median levels in patients with inflammation compared to those without, while n-acetyllysine and amino adipic acid had lower median levels in patients with inflammation.

Table 4. Numerical summary of metabolomic variables in post-session with significant differences in their medians based on inflammation=no and inflammation=yes.

Variable	Median	IQR	Median	IQR	Mann-Whitney p-value
	inflammation =No	Inflammation =No	=Yes	=Yes	statistic
N-Acetyllysine	5267	9939	1550	3945	248 0.0170
Amino adipic acid	33806	29710	21197	20038	244 0.0244
m-Coumaric acid	60008	50430	99180	82241	101 0.0487

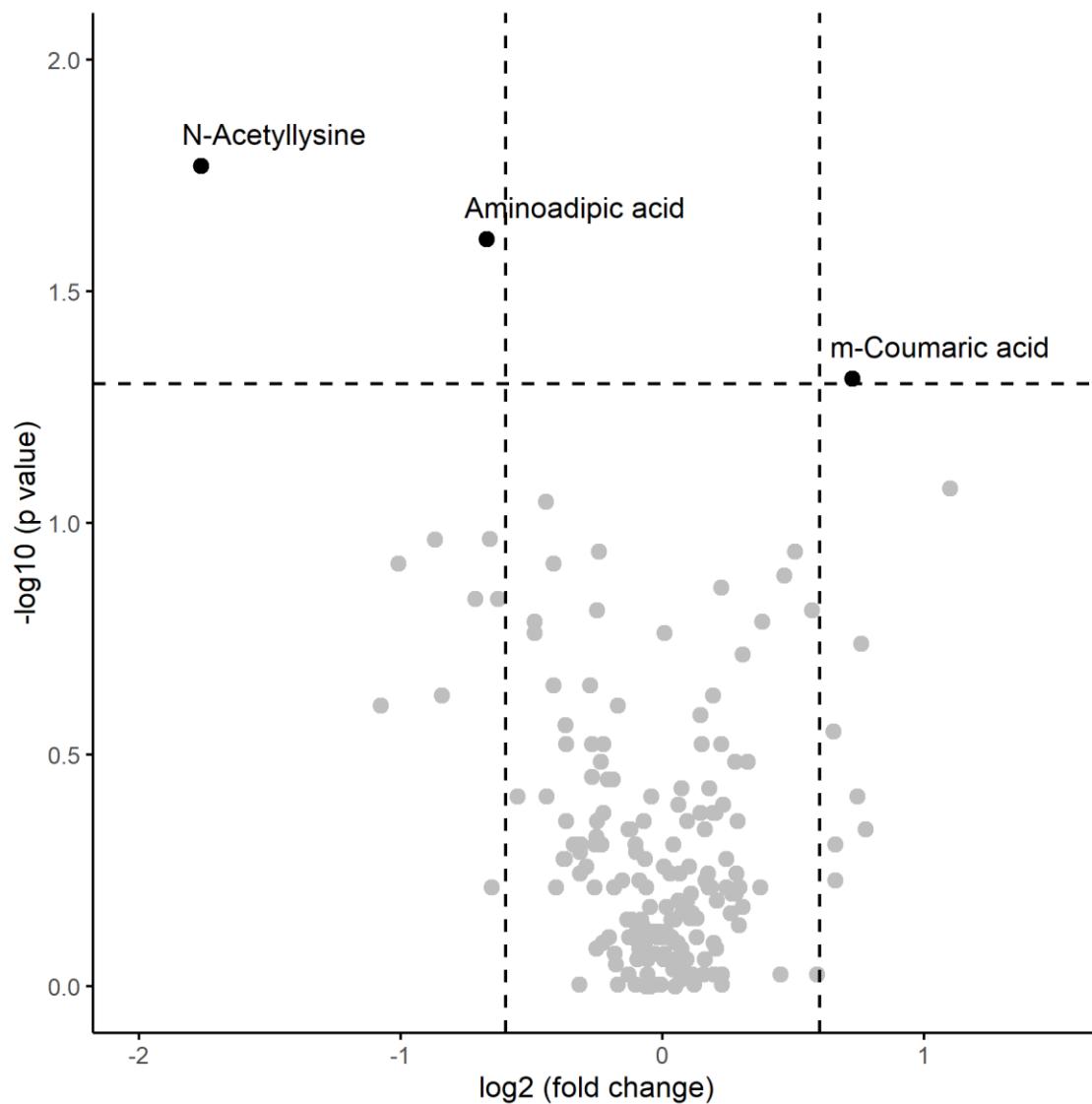


Figure 3. Volcano plot of metabolomic variables. The horizontal dashed line represents the limit of statistical significance (corresponding to p -value = 0.05); values above it denote variables with significantly different medians. The vertical dashed lines represent a $\log_2(\text{foldchange})$ of -0.6 and +0.6. Values above + 0.6 represent variables with a median for inflammation=yes that is 1.5 times in greater magnitude than for inflammation=no. Values below -0.6 represent variables with a median for inflammation=no that is 1.5 times greater in magnitude than for inflammation=yes.

However, when we performed the multivariate analysis in the post-session samples it failed to satisfactorily discriminate between patients with inflammation and those without inflammation, possibly due to the removal of a large portion of metabolites during the hemodialysis technique.

3. Discussion

Our objective was to characterize the metabolic profile observed in one year dialysis-dependent patients before and after undergoing a hemodialysis session. Omics science have seldom been used to specifically identify biomarkers related to inflammation in hemodialysis patients. We conducted a systemic search on PubMed using the terms 'hemodialysis AND metabolomics AND inflammation' and we adjusted the publication date to the last 10 years. We obtained 18 results. We dismissed four studies as they did not employ metabolomics or identify novel metabolomic biomarkers related to inflammation, three studies that explored the changes in non-dialysis-dependent patients, an article

about a novel research method that did not include results and a review article about aluminum exposure in HD patients. We reviewed the remaining 9 articles:

A study published in 2022 by Holle et al. suggested that gut barrier dysfunction and microbial metabolite imbalances in children with CKD contribute to a proinflammatory immune response as evidenced by stage-dependent elevations in serum TNF-alpha and sCD14, diminished short chain fatty acid production and increased tryptophan metabolites of bacterial origin [11].

A study published by Kim et al in 2021 compared how high-flux and medium cut-off (MCO) dialyzers affect metabolism, showing that MCO produced significant changes in metabolites (lower succinate, higher glutamate) and proteins, potentially improving oxidative stress and nutrition by eliminating medium-sized toxins [12].

Another study published in 2022 investigated endocannabinoid and oxylipin levels in female hemodialysis patients. They had lower levels of EPA and it associated oxylipins and showed elevated levels of metabolites linked to inflammation such as n-acetylethanolamides, monoacylglycerols and kynurenone and creatine [10].

Correspondingly, a study published by Tsalik et al examined the metabolome, proteome and transcriptome of 150 patients with critical illness, including patients receiving chronic HD. They identified elevated levels of phenylacetylglutamine, 4-acetamidobutanoate, and uremic retention substances, linking them to inflammation [13].

Furthermore, a 2022 study identified that elevated levels of the metabolite trimethylamine-N-oxide (TMAO) correlated with increased CRP and dialysate IL-6 in peritoneal dialysis (PD) patients suggesting exacerbated peritoneal inflammation and potentially contributing to peritonitis risk in PD patients [14].

If we consider dialysis in other contexts, such as acute kidney injury (AKI), a 2021 study examined the use of a proteomic platform to analyzed the serum samples from patients with AKI requiring hemodialysis highlighting 119 proteins associated with kidney recovery and inflammation [15].

Similarly, another study found that, in AKI critically ill patients necessitating RRT lower levels of the anti-inflammatory 1-arachidonoyl-lysoPCR and eicosatetraenoyl-lysoPCR were associated with mortality prediction by day 8 and amino acids metabolites by day 28 [16].

A different study published in 2016, found that elevated levels of the metabolite trimethylamine-N-oxide (TMAO) are closely linked with the extent of residual renal function. These levels do not change with hemodialysis but do normalize with renal transplantation [17].

In 2018, researchers used mass spectrometric glycomics to identify biomarkers in serum and dialysate samples from peritoneal dialysis patients. The study found that changes in protein N-glycosylation are linked to PD-related complications such as peritonitis and loss of peritoneal cells [18].

Our article is novel due to the use of semi-targeted metabolomics and the LASSO statistical method, which allows us to create a predictive model that distinguishes between inflamed and non-inflamed patients based on blood metabolites:

In the pre-session group, we identified indole-3-acetaldehyde as a significant variable associated with lack of inflammation in both univariate and multivariate analyses.

The breakdown of dietary proteins results in the liberation of tryptophan which is metabolized by gut microbiota in various compounds, including indole-3-acetaldehyde. Tryptophan metabolites have shown diverse beneficial effects on various health conditions, such as modulating immune responses in inflammatory bowel diseases, influencing carcinogenesis through interactions with the gut microbiota, regulating inflammation and metabolism in obesity and metabolic syndrome, limiting nervous system inflammation, contributing to the immune response against infectious diseases, affecting vascular inflammation and cardiovascular health [19]. However, unlike what occurs in our study, indole-3-acetaldehyde has been shown to contribute to inflammation in other studies by modulating the balance between anti-inflammatory regulatory T-cells and pro-inflammatory Th17 responder cells in the gut, while also influencing the adaptive immune response through alterations in TGF- β sensing and T cell receptor signaling [20,21].

Although the evidence on whether indole-3-acetaldehyde has beneficial or detrimental effects on inflammation associated with various diseases is unclear, it appears that it has a protective effect on hemodialysis patients according to the results of our study.

In the univariate analysis, the variables identified as associated with lack of inflammation were 2-ketobutyric acid and urocanic acid.

2-ketobutyric acid, also referred to as alpha-ketobutyrate or 2-oxobutyrate, falls within the category of short chain keto acids and derivatives, characterized by ketoacids with alkyl chains containing fewer than 6 carbon atoms. It participates in the metabolic pathways of various amino acids, propionate metabolism, and C-5 branched dibasic acid metabolism. It is a degradation product of threonine and can be converted into propionyl-coA. Subsequently, propionyl-coA can be transformed into methylmalonyl coA, which feeds into the citric acid cycle as succinyl coA, an intermediate [22].

In a study published in 2022 supplementation with alpha-ketobutyrate extended the lifespan of *Caenorhabditis elegans* (*C.elegans*) and delays senescence in fibroblast cells. This effect is likely mediated by an increase in NAD⁺ via LDH-1, leading to SIR-2.1/SIRT1-dependent enhancement of peroxisome function and biogenesis. Increased peroxisome function promotes autophagy, which contributes to longevity and delays cellular senescence [23]. This observation aligns with the findings in our study.

Urocanic acid, derived from histidine breakdown, is abundant in the skin's outer layer. It absorbs UV light, converting to an immunoregulator. Initially thought to shield against UV-B, further research reveals its role in suppressing hypersensitivity and enhancing skin graft survival. UA's potential spans from UV protection to immunomodulation [22,24]. Another study observed that human retinal pigment epithelial cells treated with cis-urocanic acid had increased levels of cytoprotection, decreased levels of inflammatory cytokines and lower DNA damage [25].

Although there are no studies showing similar effects of urocanic acid in hemodialysis patients, it seems physiologically plausible that this metabolite is associated with low levels of inflammation in this population.

On the other hand, the multivariate analysis identified the metabolites allantoin, taurodeoxycholic acid, norepinephrine, pyroglutamic acid and L-hydroxyproline as capable of discriminating patients with an inflammatory profile.

Allantoin is a diureide of glyoxylic acid. Alternatively known as 5-ureidohydantoin or glyoxyldiureide, it is generated through the oxidation of uric acid. Allantoin serves as an indicator of oxygen -free radical load arising from the non-enzymatic interaction between uric acid (UA) and reactive oxygen species (ROS). The creation of allantoin needs myeloperoxidase, superoxide, and hydrogen peroxide. The first changes urate in the blood into allantoin as a final stable product. In the presence of superoxide urate radicals form hydroperoxide and in their absence they are readily reduced to urate. At sites of excess oxidative stress, however, urate radicals will promote detrimental oxidative reactions [26]. Furthermore, it can also arise from uric acid through enzymatic catalysis by uricase, which is not naturally present in humans but may exist in gut bacteria. In end-stage renal disease, higher levels of allantoin are observed, alongside a greater presence of uricase containing bacteria [27].

Finally, a notable correlation has been noted between initial serum concentrations of allantoin and mortality in two extensive human chronic kidney disease cohorts, spanning median follow-up periods of 16.5 and 9.7 years. The mean measured GFR was 30 ml/min and 47 ml/min [28].

Therefore, our study is consistent with previous observations reporting an increase in uricase-producing bacteria at the intestinal level in patients with ESRD. However, it also confirms the role of allantoin as an inflammatory marker.

Taurodeoxycholic acid, synthesized in the liver through the bonding of deoxycholate with taurine, typically exists as a sodium salt. These bile acids are steroid acids [22]. Exogenous administration of taurine conjugated bile acids has been linked to increased vasodilation by enhancing nitric oxide (NO) production from the endothelium and thus offer promising strategies for treating endothelial dysfunction in cardiovascular disease [29]. In a study published in 2020, it

was found that in individuals with type 2 diabetes mellitus (T2DM), there is a significant increase in the levels of this molecule compared to age- and gender-matched individuals without T2DM [30]. Consequently, it is possible that the endogenous production of this acid could be related to the physiological response to inflammation and could function as a biomarker in this type of patients, although its exogenous administration has beneficial properties.

Norepinephrine or noradrenalin originating from the adrenal medulla, is the precursor to epinephrine and it serves as the primary transmitter in the majority of postganglionic sympathetic nerve fibers and in the diffuse projection network originating from the locus ceruleus in the brain [22]. According to the European Uremic Toxin Working Group, norepinephrine has been recognized as a uremic toxin [31]. Research has shown that the sympathetic nervous system plays a role in chronic inflammation in conditions such as colitis, multiple sclerosis, systemic sclerosis, lupus erythematosus, and arthritis, both in animal models and humans. The overactivity of this system contributes to the development and the extension of several inflammatory conditions [32]. Hemodialysis is a clear inflammatory condition, and subsequent activation of the sympathetic system could contribute to worsening the situation for these patients.

Pyroglutamic acid, also known as 5-oxoproline, is an organic endogenous acid that can increase with prolonged administration of paracetamol at therapeutic levels, triggering metabolic acidosis characterized by an elevated anion gap. This scenario often arises in individuals facing malnutrition, infections, antibiotic treatment, renal dysfunction, or during pregnancy. Various factors affecting glutathione metabolism can explain this accumulation. Firstly, the depletion of glutathione (due to paracetamol ingestion, malnutrition or pregnancy) can ensue an ATP-depleting futile pyroglutamic acid cycle. Secondly, the excretion of the acid can be impaired due to decreased renal excretion [33].

Research published in 2019, revealed elevated pyroglutamic acid and decreased glutathione levels in septic patients, the latter being correlated to severity parameters in critically ill patients with septic shock [34]. A study published in 2024, which explored the causal relationship between gut microbial taxa, human blood metabolites and serum inflammatory markers, revealed that pyroglutamic acid contributes to elevated IL-6 and SAA1 levels [35]. Conversely, another study published two years earlier identified the compound as a potential biomarker for sepsis and systemic inflammatory response syndrome [36]. Considering the impaired renal excretion and chronic inflammation common in dialysis patients, it's logical for them to exhibit elevated levels of pyroglutamic acid.

L-hydroxyrotoic acid is an alpha amino acid that can be synthesized from ureidosuccinic acid through the catalytic activity of the enzyme CAD protein. Additionally, the conversion of L-dihydrorotoic acid and quinone into rotoic acid is facilitated by the mitochondrial enzyme dihydrorotoate dehydrogenase [22]. It seems unlikely that L-hydroxyrotoic acid would be increased in inflamed individuals due to low activity of the dihydrorotoate dehydrogenase enzyme, as inhibition of this enzyme is associated with the improvement of various inflammatory conditions [37–39]. However, this inflammatory activity could indeed be explained by the overactivity of the CAD complex, which enables activation of memory T cells and cytokine production through the novo pyrimidine synthesis [40]. Moreover, inhibiting this complex proved to be beneficial in inflammatory situations such as COVID infection [41] or certain types of cancer [42].

Finally, the multivariate analysis identified benzoic acid, indole-3-acetaldehyde, methionine, citrulline, alpha-ketoglutarate, N-acetyl-L-ornithine and 3,4-dihydroxybenzenacetic acid as useful for the identification of non-inflamed patients.

Benzoic acid (BA) is naturally present, both in its free form and as esters in many plant and animal species. Appreciable amounts have been found in most berries. BA ingestion has been found to increase nutrient digestibility and to decrease ammonia nitrogen levels in the gut. Furthermore, it enhances mucosal integrity and promotes intercellular junction formation, as well as influencing immunological responses and microbiota [43]. Hippuric acid is the excreted form of benzoic acid. Benzoic acid undergoes metabolism through butyrate-CoA ligase, producing an intermediate compound called benzoyl-CoA, which is subsequently metabolized by glycine N-acyltransferase to form hippuric acid. The protection that appears to be provided by the presence of benzoic acid could

also be related to the decrease in activity of this pathway, which would result in lower levels of hippuric acid. Hippuric acid in advanced CKD has been associated with atherogenesis through the disruption of the endothelial function and renal fibrosis [44–46].

Methionine, an indispensable amino acid containing sulfur, plays a crucial role in synthesizing key molecules including antioxidants like glutathione, along non-essential aminoacids such as carnitine and cysteine, as well as methyl donors like S-adenosyl methionine and vasodilatory intermediates. Eggs, sesame seeds, fish, meat, and cereal grains are among the primary sources of methionine [47]. Methionine supplementation can modulate inflammation and oxidative stress reducing the expression of inflammatory and fibrogenic genes while enhancing endogenous antioxidant capacity and protecting against oxidative damage [48–50].

However, research has also indicated that limiting methionine can boost glutathione production curbing oxidative stress and some studies have found that restricting this substance in mice results in decreased oxidative stress, albeit without changes in antioxidant enzyme activity [51,52].

Similarly to what occurs with indole-3- acetaldehyde, it remains uncertain whether methionine has beneficial or detrimental effects on inflammation associated with various diseases, our study indicates a protective effect on hemodialysis patients.

Citrulline is an important metabolite in the arginine metabolism. Asymmetric dimethylarginine (ADMA) is a metabolite derived from arginine and can inhibit nitric oxide synthase (NOS), thereby limiting the production of nitric oxide and potentially leading to vascular complications associated with end-stage renal disease. ADMA is primarily metabolized by dimethylarginine dimethylaminohydrolases (DDAH-1 and DDAH-2) and converted into dimethylamine and citrulline. Patients with kidney dysfunction can have lower concentrations of DDAH-1, which is particularly abundant in the kidney, therefore impeding the further metabolism of citrulline in the arginine-NO pathway. Elevated levels of ADMA are associated with cardiovascular disease, hypertension and immune dysfunction [53]. Therefore, we could argue that patients with increased citrulline have better preserved metabolism of arginine and nitric oxide, and thus, the presence of this metabolite is related to the absence of inflammation. Other studies focusing on patients performing hemodialysis have also found higher citrulline levels. [10] This metabolite has been shown to be significantly reduced after hemodialysis session in adults with ERSD, which may signal an impaired NO synthesis post-procedure [54]. That is possibly the reason why the levels of this metabolite were not significantly associated with the absence of inflammation in the post-hemodialysis examination, as its levels have been reduced to nearly zero. Additionally, citrulline levels can be increased with the exogenous administration of L-carnitine in patients undergoing chronic hemodialysis [55].

Alpha-ketoglutarate (AKG) is an important intermediate of various metabolic pathways including tricarboxylic acid (TCA) cycle, anabolic and catabolic reactions of amino acids, and collagen biosynthesis [56].

Recently there have been several reported health-promoting effects of AKG, including anti-aging, extension of healthy lifespan, anti-osteoporotic, anti-inflammatory, and anticarcinogenic effects, as well as protection against pressure overload cardiomyopathy. These beneficial effects are not only metabolic but also mediated through epigenetic mechanisms [57]. Specifically, it has been recognized as an antioxidant agent, enhancing the activity of other antioxidant enzymes such as SOD, CAT, and glutathione peroxidase. Other antioxidant mechanisms of AKG include the decomposition of hydrogen peroxide and the promotion of mitophagy to clear damaged mitochondria [56]. However, it is important to note that recent research has shown that AKG can induce ROS through autophagy induction [58].

AKG is widely considered safe and bioavailable, making oral or intravenous supplementation of AKG an effective therapeutic approach [56]. Additionally, SGLT inhibitors have been shown to increase renal levels of AKG, which may be another factor to explain their cardiovascular benefits [59].

In summary, it makes sense that AKG is associated with reduced inflammation in hemodialysis patients, and furthermore, it suggests a potential therapeutic target in these individuals.

It is remarkable that although alpha-ketoglutarate can be formed from several aminoacids one of the pathways starts in histidine. Histidine is an essential amino acid that is obtained from meat

and other high protein products. Histidine is oxidized and deaminated to urocanic acid by the enzyme histidase. Urocanic acid is subsequently hydrolyzed to form N-formiminoglutamate (FIGu). This compound binds to tetrahydrofolate, releasing glutamate. Finally, glutamate is degraded to alpha-ketoglutarate [60].

Both urocanic acid and alpha-ketoglutarate help us distinguish the group of non-inflamed patients, suggesting that the activation of this metabolic pathway may confer some protection to patients on hemodialysis. At this stage of kidney disease, the protein needs of patients increase to 1,3 g/kg/day, so changes in the diet could help explain these observations. In Figure 4, we observe the relationship of urocanic acid, alphaketoglutarate and 2-oxybutyrate with the Krebs cycle, the increase in autophagy, mitochondrial biogenesis, and their connection to the reduction of the inflammatory environment.

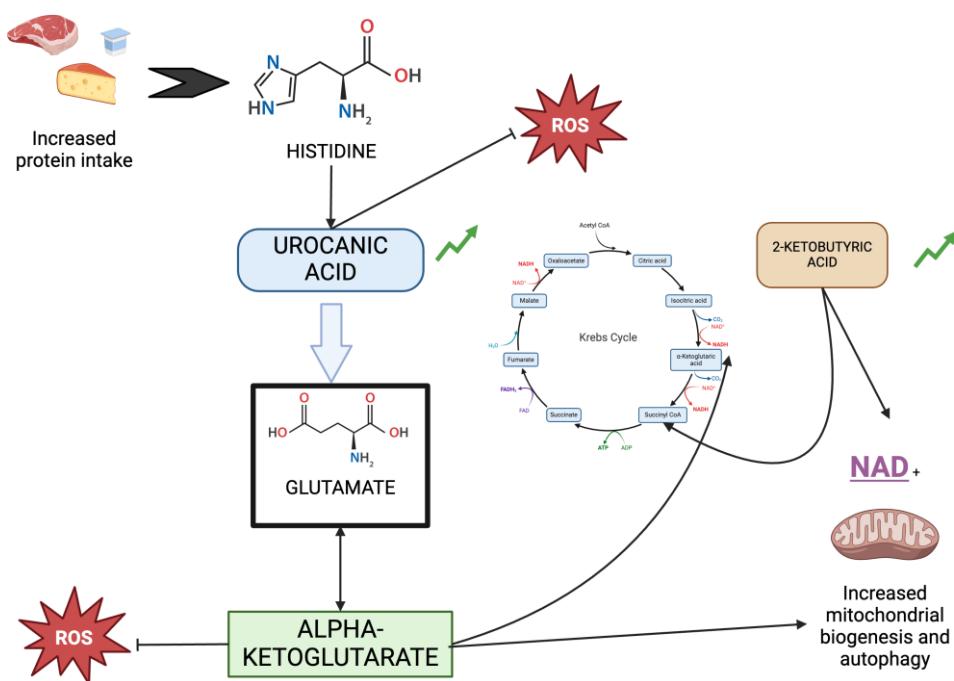


Figure 4. Relationship of urocanic acid, alpha-ketoglutarate, and 2-oxobutyrate with the Krebs cycle, autophagy and mitochondrial biogenesis.

Within the ornithine cycle, ornithine serves as the direct substrate and n-acetylornithine is a N-acetylation derivative, which can also serve as a precursor of ornithine [22]. The ornithine cycle is a pivotal amino acid metabolic pathway linked to various diseases such as infection [61], cancer [62] and hypertension [63]. A study published in 2021 found that n-acetyl-ornithine was positively correlated with multiple cytokines and coagulation indices in COVID-19 patients, especially those with severe cases [64]. Currently, there are no cases in literature that associate this metabolite with protective characteristics against inflammation. However, other studies suggest that oxidative stress upregulates the transcription of enzymes such as ornithine decarboxylase which produces an increase in polyamines, such as spermine and spermidine [65]. Diabetic rats have lower levels of spermine and spermidine, which cause heart damage and inflammation, leading to fibrosis. Spermidine treatment showed promising results in reversing this harmful processes [66]. Another study found that ornithine, through its conversion to putrescine via Arg 1 and ornithine decarboxylase, plays a critical role in enhancing continual efferocytosis by macrophages. This metabolic pathway supports the optimal clearance of apoptotic cells and promotes the resolution of tissue injury [67]. Therefore, the fact that N-acetylornithine levels are associated with the absence of inflammation could indicate a more conserved polyamine metabolic pathway and, consequently, a better response to inflammation.

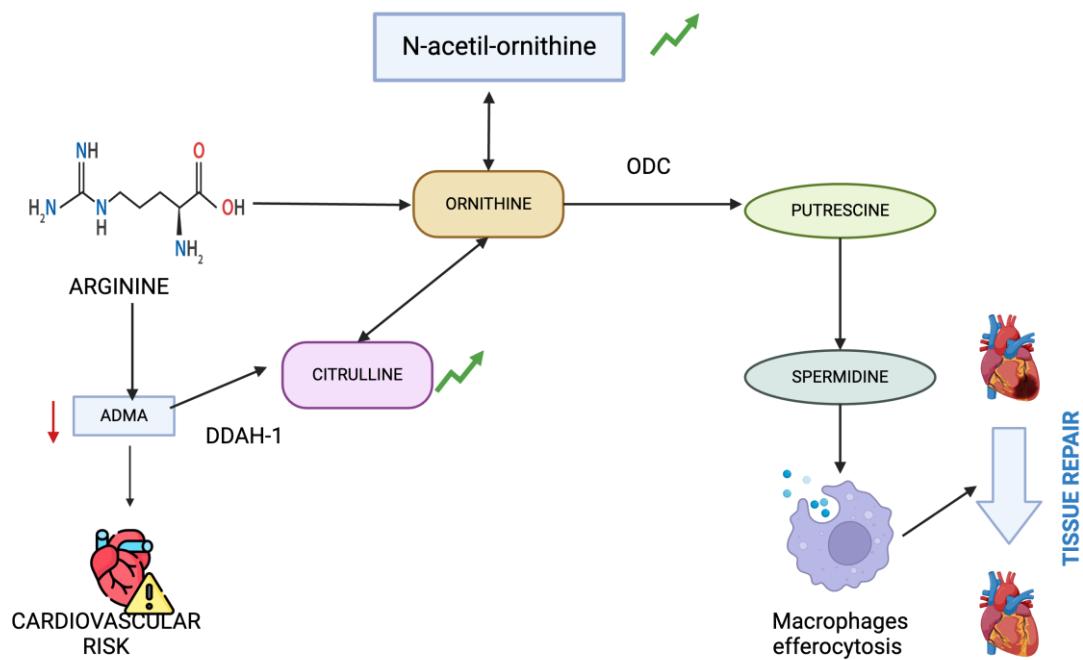


Figure 5. Metabolic pathways involving citrulline and n-acetylornithine highlighting their roles in arginine metabolism and polyamine synthesis influencing inflammation and tissue health.

A 2022 study, 3,4-dihydroxybenzeneacetic acid also known as 3,4-dihydroxyphenylacetic acid or DOPAC/DHPAA demonstrated a partial reversal of pro-inflammatory microRNA responses in human intestinal epithelial cells exposed in cranberry extract [68]. Conversely, another study published in 2020, highlights the anti-inflammatory potential of epicatechin and dihydroxybenzoic acid from cocoa in alleviating diabetic kidney inflammation through targeted cellular pathways, contrasting with the lack of similar effects observed with 3,4-dihydroxyphenylacetic acid [69].

Finally, DOPAC/DHPAA is a metabolite of dopamine and its reduction indicates dopamine dysfunction in Parkinson's disease. In an article published in 2023, it was found that empagliflozin treatment restored this metabolite levels which suggest a potential stabilization of dopaminergic function [70].

In the post-session samples, m-coumaric acid levels were higher in inflamed patients compared to non-inflamed patients, whereas n-acetyllysine and amino adipic acid levels were lower in inflamed patients.

M-coumaric acid, alternatively referred to as 3-coumarate, is a hydroxycinnamic acid. Its presence in human biofluids is influenced by dietary intake, particularly from whole grain consumption [22]. In an in vitro study published in 2011 it was found that m-coumaric acid had pro-oxidative and pro-glycative properties, suggesting a potential detrimental role under conditions involving high levels of glycation inducing agents like methylglyoxal [71]. Moreover, in a study performed in rats showed that metabolites of coumaric acids like dihydro-3-coumaric acid may play a role in Alzheimer's disease [72].

N-acetyllysine is a n-acetyl aminoacid which can be classified as uremic toxins if present in high concentrations in serum or plasma contributing to kidney damage, cardiovascular disease, and neurological deficits if not properly eliminated by the kidneys [73]. Nonetheless, newer studies have found that posttranslational modification such as acetylation of histone proteins within chromatin are dynamically regulated in response to DNA damage. Acetylated lysine residues serve as a binding site for acetyl-lysine reader proteins, which interpret acetylation signals during DNA damage and

have a pivotal role in genome maintenance and repair processes critical for cellular health and disease prevention [74], which would be consistent with our results.

Aminoadipic acid, also known as alpha-aminoadipic acid and L-alpha-aminoadipic acid has been identified as a marker for metabolic dysfunction and diabetes risk [75]. It has been found to correlate with other inflammatory diseases such as gout [76], ischemic heart failure [77] and community-acquired pneumonia [78]. However, in another study published in 2019, it was used to impair the function of astrocytes, revealing the role these cells play in sustaining neuroinflammation and contributing to dopaminergic neuronal loss in a model of Parkinson's disease [79]. In any case, as can be seen in Figure 3, the clinical magnitude difference for distinguishing the non-inflamed group was very small for this metabolite and was not confirmed in the multivariate analysis.

The fact that dialysis was able to reduce the concentration of many of the metabolites studied makes the analysis in this group of patients difficult.

In comparison with our previous study analyzing inflammation associated metabolites in stage 5 non-dialysis dependent CKD patients, we continue to observe the significance of mitochondrial energy metabolism. However, in this case, patients with preserved metabolic pathways that promote autophagy and mitochondrial biogenesis appear to be more protected against inflammation. Additionally, the metabolism of arginine, the urea cycle and the microbiota, which interacts with several metabolic pathways seem to play an important role [80].

This study has several limitations. Firstly, our data only indicate trends or changes in response intensities rather than precise concentrations. Secondly, we opted to use an in-house library of polar compounds to streamline results and interpretation, which may have led to the omission of some metabolites. Lastly, due to time and budget constraints we were limited in our sample size, restricting the scope for multiple comparisons and subgroup analysis.

Due to this limitations, future research should expand these findings to validate identified biomarkers and explore their clinical utility in larger patient cohorts, potentially paving the way for personalized therapeutic interventions aimed at mitigating inflammation in hemodialysis patients.

4. Materials and Methods

Experimental Design and Cohort

Our objective was to investigate the influence of various metabolites on inflammation in patients who had undergone one year of chronic hemodialysis. We conducted an observational prospective, single-center study, where we gathered the patient's clinical and analytical data and information about the hemodialysis sessions.

Initially, we conducted a descriptive analysis of the study population to characterize its demographics. Subsequently, we explored the metabolomic profiles of the patients before and after the hemodialysis session through the use of liquid chromatography and high-resolution mass spectrometry.

The inclusion criteria comprised age over 18 years and to have been undergoing hemodialysis sessions for more than a one year at the Hospital La Fe or at a peripheral dialysis center affiliated with it. Exclusion criteria included suboptimal initiation due to clinical instability (defined as acute decompensation requiring hospitalization, requiring temporal CVC insertion or unexpected and unwanted change in techniques).

We collected data about age, gender, height, weight, BMI, cardiovascular risk factors, urea, uric acid, corrected calcium for serum albumin, phosphate, sodium, potassium, chloride, CRP, hemoglobin, leucocytes and platelets. Regarding the hemodialysis session, we collected data on the type of technique employed, the access used, the residual diuresis at the start of the procedure, the average interdialysis weight gain, and the Kt/V to ensure efficacy.

Metabolomics Analysis

The processing of the samples was similar to that conducted in the article published by our group this year [80].

The serum centrifuged from the samples was collected and stored at -80°C and subsequently, a procedure for protein precipitation and the extraction of polar compounds was performed by adding 180 microliters of cold methanol to 20 microliters of the serum. After a double centrifugation at 13000 g (10 min, 4°C), 20 microliters of the supernatant were transferred to a 96-well plate for liquid chromatography coupled to mass spectrometry analysis. Additionally, 70 microliters of water and 10 microliters of the standard mix solution (reserpine, leucine, enkephalin, phenylalanine-d5, 20 microM) were added to each sample. Quality control samples were prepared by mixing 10 microliters from each serum sample. Blank samples were prepared by replacing serum with ultrapure water to identify potential artifacts. Finally, plasma samples, QCs, and blanks were injected into the chromatographic system. To minimize intrabatch variability, there was a random injection order and an analysis of quality samples every six plasma samples, with blank analysis conducted at the end of the sequence.

Ultra-Performance Liquid Chromatography-High Resolution Mass Spectrometry (UPLC-HRMS) analysis was conducted using an Orbitrap QExactive spectrometer (ThermoFisher) coupled to a Ultra-Performance Liquid Chromatography (UPLC) system. Chromatographic separation utilized a Xbridge BEH Amide column (150x2mm, 2.5 microliter particle size; Waters) with a runtime of 25 minutes, an injection volume of 5 microliters, and a column temperature set at 25°C. The autosampler was maintained at 4°C, and a flow rate of 105 microliters/min was achieved using water and 10 mM ammonium acetate as Mobile Phase A, and acetonitrile (ACN) as Mobile Phase B. The gradient protocol included various proportions of Mobile Phase B, starting at 90% and gradually decreasing to 0% over the course of 25 minutes.

Electrospray ionization was utilized in both positive and negative modes (ESI +/-) for full mass acquisition, with a resolving power of 140,000. Two events were employed: one covering mass ranges from 70-700 Da, and another covering mass ranges from 700-1700 Da. Data were acquired in centroid mode.

Data preprocessing involved converting raw data to mzXML format using mass converter, followed by processing in EI-MAVEN software to generate a peak table containing m/Z values, retention times, and intensity of polar compounds. Peak areas were extracted and annotated using an in-house polar compound library. Data from positive and negative modes were combined for statistical analysis.

Before conducting statistical analysis, data quality was assessed by evaluating internal standards stability and coefficients of variation (CV) of quality control samples. Molecular features with CV > 30% were excluded from the data matrix, and normalization method (LOESS) was applied to mitigate intrabatch variability resulting from technical differences. The filtered peak table was then used for subsequent statistical analysis.

Statistical Analysis

Patients with CRP values \leq 2 mg/L were categorized as non-inflamed, while those with CRP $>$ 2 mg/L were considered inflamed. We determined this value cut point based on the identification of CRP levels between 1-3 mg/L as the grey zone of inflammation, where cardiovascular risk could possibly increase. [81] All the patients underwent a systematic medical and basic physical examination before the sample examination to ensure the influence of clearly infectious events was minimal.

Initially, we conducted a univariate analysis to explore which metabolomic variables correlated with the presence of inflammation. This involved identifying metabolites significantly upregulated with a fold change of 1.5 in the inflammatory group compared to the non-inflammatory group using a non-parametric Mann-Whitney test ($\text{log2(foldchange)} = \text{log2(MInflammation=1/Mnoninflammation=0)}$).

For the multivariate analysis, we employed a logistic regression model, suited for binary response variables, applying LASSO regularization. LASSO (Least Absolute Shrinkage and Selection Operator) is a regularization technique aiding in variable selection and regularization by shrinking some regression coefficients towards zero, thus facilitating a more interpretable model. This algorithm optimized the coefficients of logistic regression for each variable (standardized) to enhance

performance, specifically reducing classification errors. This was achieved by progressively diminishing coefficients using a multiplier parameter in the algorithm's cost function until they reached zero, effectively eliminating the corresponding variable. The extent of coefficient minimization and elimination was determined by an additional parameter called lambda. A higher lambda value led to a greater coefficient penalization, reducing their values to zero, and consequently, reducing the number of variables included in the model. The optimal lambda value was determined using a leave-one-out cross-validation. Various models were fitted, with one group of subjects excluded in each iteration to estimate their classification into the 'inflamed=no' or 'inflamed=yes' group. The error for each case was calculated, and the lambda value minimizing this error was considered the optimal choice. In this model, k was set to 50, implying one patient was excluded for estimation. In each iteration, with a focus on minimizing classification errors. Standardized coefficients and Odds Ratio were computed for each variable. ORs represent the multiplier for the probability of belonging to the inflammation=yes group compared to inflammation no assuming a one standard deviation increase in the variable, as we use standardized coefficients.

The sign of the coefficients indicates how changes in variables affect the probability of inflammation. Positive coefficients imply a higher likelihood of inflammation, while negative coefficients decrease the probability. Variables with larger absolute standardized coefficients hold higher impact in the model, as reflected in their odds ratios (OR= $e^{\text{coefficient}}$).

5. Conclusions

Our study introduces novel findings through the application of semi-targeted metabolomics and the LASSO statistical method, enabling the creation of a predictive model distinguishing inflamed hemodialysis patients. Non-inflamed patients seem to have a preserved autophagy and less mitochondrial dysfunction. Moreover, the metabolism of arginine and therefore the urea cycle are pivotal to the understanding of inflammation in this group of patients. Finally, the microbiota, along with uricase producing bacterial and those that metabolize tryptophan play a crucial role.

These results allow us to identify metabolic pathways related to inflammation in hemodialysis patients, thereby identifying potential therapeutic targets and points of optimization in renal replacement therapy.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Polar metabolites.

Author Contributions: Conceptualization, M.P-F, M.R-M and J.H-J; methodology, M.P-F M.R-M, J.A.L. and A.B-T.; software, M.R-M, J.A.L. and A.B-T.; formal analysis, M.R-M, J.A.L. and A.B-T.; investigation, M.P-F; writing—original draft preparation, M.P-F; writing—review and editing, M.P-F, M.R-M, J.A.L., I.V-B and A.B-T.; visualization, M.P-F, M.R-M, J.A.L., I.V-B, A.B-T, J.H-J, R.D-S, A. S-O and P.S-P; supervision, J.H-J.; funding acquisition, M.P-F. All authors have read and agreed to the submitted version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Hospital Universitario y Politécnico la Fe (protocol code 2019-232-1 and date of approval 29th January 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data on which the article is based are available as Supplementary Materials.

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Conflicts of Interest: The authors declare no conflicts of interest.

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