SOLUBLE TLR4 IN HEMODIALYSIS PATIENTS

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OBJECTIVES

Toll-like receptors (TLRs) play a fundamental role in the innate immune system by triggering proinflammatory pathways.

TLR4, the best-characterized TLR, binds to LPS of gram-negative bacterial cell walls. Upon binding of LPS to TLR4, the adaptor protein myeloid differentiation factor 88 (MyD88) is recruited to the Toll/IL-1 receptor (TIR) domain of the receptor.

In patients on hemodialysis (HD)TLR4 is highly expressed and is a strong candidate as a mediator of systemic inflammation in HD.

Recently, a **soluble form of extracellular TLR4 domain (sTLR4)** has been characterized, which has shown the ability to attenuate TLR4 signalling.

The presence and the role of sTLR4 in HD has not been investigated, so far.

Here we studied the profile **of sTLR4 in regular HD patients.**

METHODS

- Forty patients on maintenance HD for at least for 6 months were included in a cross sectional study.

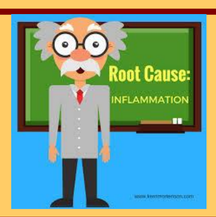
- We enrolled both patients undergoing standard bicarbonate HD (BHD) or on-line hemodiafiltration (HDF). Sex-matched healthy subjects were the control group.

- We collected clinical and biochemical data, including C-reactive protein (CRP).

- According to CRP levels the patients were stratified **in inflamed (i.e. CRP ≥ 1 mg/dl) and non-inflamed subjects (i.e. CRP < 1 mg/dl)**.

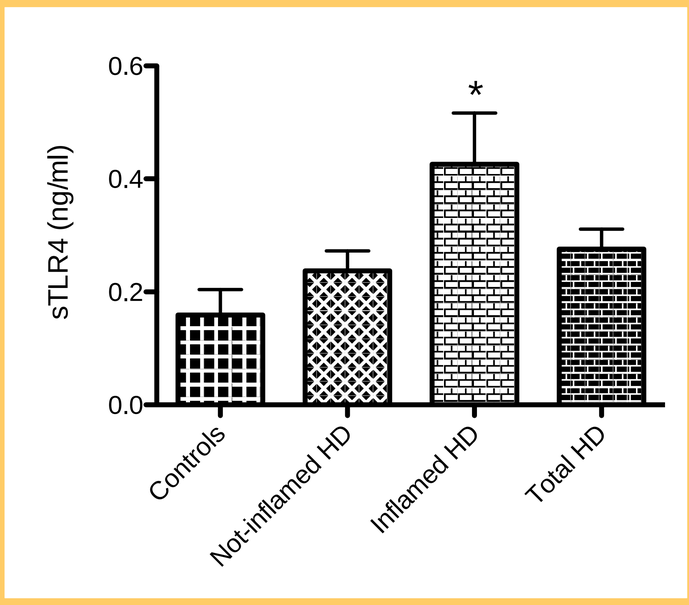
- Body composition was studied by BCM (FMC, Bad Homburg, Germany), which expresses body composition as a three-compartment model, providing overhydration (OH), lean (LTI), and fat tissue index (FTI).

- In each patient, before and after the hemodialysis session, serum was withdrawn and tested for **sTLR4 levels** by an ELISA kit.



RESULTS

Inflamed HD patients presented significantly higher **sTLR4** levels than healthy subjects and non-inflamed HD patients (0.42±0.25 vs 0.23±0.19 ng/ml, p<0.05).

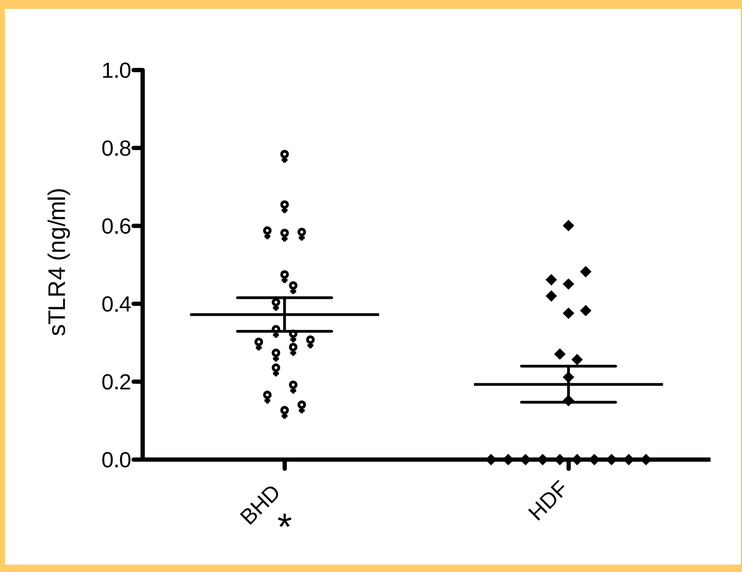


Correlation analysis showed a **direct** association between predialysis **sTLR4** and **BMI, FTI triglycerides and CRP**, whereas there was a significant **inverse** association with **LTI and albumin** In multivariate analysis, after adjustment for age and time on dialysis, sTLR4 resulted significantly directly associated with FTI (p=0.038).

N= 40	Age	Dialysis vintage	sTLR4	BMI	FTI	FTI/BMI	LTI	CRP	Albumin
Age	1								
Dialysis vintage	-0.1	1							
sTLR4	0.14	0.039	1						
BMI	-0.1	-0.15	0.43*	1					
FTI	0.18	-0.14	**0.55 §**	**0.79 §**	1				
FTI/BMI	0.29	-0.16	**0.54 §**	**0.66 §**	**0.9§**	1			
LTI	**-0.47 §**	0.11	**-0.52 §**	-0.18	**-0.67 §**	**-0.8 §**	1		
CRP	0.24	0.07	**0.52 §**	0.05	0.31	0.36 *	-0.47 §	1	
Albumin	-0.07	0.15	-0.4*	-0.05	-0.24	-0.28	-0.09	-0.32 *	1

* p <0.05, § p <0.01

sTLR4 levels in patients undergoing **BHD** resulted significantly higher than those measured in patients undergoing **HDF** (0.37±0.18 vs 0.19±0.21 ng/ml, p<0.05)

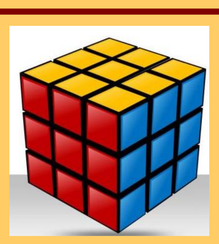


CONCLUSIONS

In HD sTLR4 levels are associated with inflammatory and nutritional parameters, suggesting that this molecule could be a part of the counter-regulatory system developed to modulate inflammation in HD.

The demonstration of the presence of sTLR4 in HD and the study of its role might offer new therapeutic options to face the unsolved problem of inflammation and malnutrition in HD.

Many crucial questions, such as the precise biological functions of sTLR4, the effect of different dialysis treatments and the impact of TLR4 pathway modulation in HD patients, remain open and worthy of specific-designed studies.



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