

Original Article

Levels of hepatocyte growth factor in serum correlate with quality of life in hemodialysis patients

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Abstract: Purpose: Patients with end stage renal failure (ESRD) report low quality of life and inflammation may be one of the contributing factors. We studied if the hemodialysis induced inflammation correlates with the patients quality of life. Methods: Study was performed in 76 (35 males and 41 females) ESRD patients treated with hemodialysis. Effect of one dialysis session on blood concentration of Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), Interleukin 6 (IL6) and Monocyte Chemoattractant Protein-1 (MCP-1) was studied. Results were correlated with answers given by patients to a short questionnaire composed of questions from Kidney Disease Quality of Life Short Form (KDQoL-SF) questionnaire. Results: Hemodialysis induced increase of serum level of HGF (+117%) and IL-6 (+17%). Declared by patients health status correlated with their age, GFR, kt/V and hemodialysis induced change in serum IL6 and HGF level ($R^2 = 0.469$, $P < 0.001$). Physical activity correlated with age, serum IL-6 and hemodialysis induced change in serum HGF and VEGF ($R^2 = 0.362$, $P < 0.001$). Presence of social/mental problems during previous 4 weeks correlated with age, serum HGF and hemodialysis induced changes in serum HGF and VEGF levels ($R^2 = 0.333$, $P < 0.001$). Interference of the kidney disease with daily life activities correlated with age, serum VEGF and hemodialysis induced change in serum HGF and IL6 levels ($R^2 = 0.422$, $P < 0.001$). Conclusion: Inflammation correlates with reduced quality of life in ESRD. Low hemodialysis-induced release of the anti-inflammatory cytokine HGF correlates with impaired quality of life in that group of patients.

Keywords: Uremia-hemodialysis, quality of life, inflammation, hepatocyte growth factor

Introduction

Inflammation is a common feature of uremic syndrome in patients with chronic renal failure. Intensity of that process determines not only risk of mortality, but also progression of decline of the renal function and cardiovascular complications [1]. Besides effect of uremia *per se*, also renal replacement therapy with hemodialysis is enhancing the systemic inflammatory response and similar effect is caused by peritoneal dialysis [2, 3]. High levels of the circulating proinflammatory cytokines are associated with increased mortality in ESRD patients treated with hemodialysis [4]. Hemodialysis induced inflammation can be due to activation of complement by cuprophane or other cellulose dialysis membranes [5]. Intensity of the hemodialysis bioincompatibility may also depend on the

genetic predisposition, which determines intensity of the inflammatory response after exposure to the stimulant [6]. Therefore hemodialysis induced inflammatory response is probable not identical in all patients.

There is a debate if the inflammatory reaction in ESRD patients, which predicts risk of mortality [4] also affects quality of their life. Uden et al. found in primary health care patients, with normal renal function, correlation between increased blood cytokines levels and deteriorated self-rated health [7]. Progression of the renal failure results in gradual deterioration of the patients health-related quality of life (HRQoL) and increased blood C Reactive Protein (CRP) level, together with cardiovascular disease were the strongest predictors of these changes [8]. Anand et al. found in a group of

HGF and quality of life in hemodialysis patients

266 patients starting dialysis inverse correlation between self-reported physical activity and CRP level [9]. In another study in a group of 917 incident dialysis patients low vitality score correlated with higher CRP blood levels [10]. On the other hand, Spiegel et al. in a systematic review of literature on biomarkers of HRQoL in ESRD found no strong correlation between inflammation and deterioration of the patients HRQoL [11]. We hypothesized that acute inflammatory response caused by procedure of hemodialysis may be a good index of intensity and quality of the systemic inflammation in ESRD patients.

In the present paper we show results of our study in which we looked at correlation between pattern of the hemodialysis-induced inflammatory response and various aspects of quality of life of patients with ESRD.

Material and methods

Research protocol was approved by the University Ethical Committee. 76 patients: 35 males and 41 females, after giving the informed consent, were enrolled into the study. Patients with diabetes mellitus, neoplastic diseases, liver diseases or active systemic inflammatory diseases were excluded from the study. Mean age of the patients was 62.0 ± 18.0 years and patients were treated with hemodialysis mean for 26.5 ± 15.1 months. Mean value of the patients glomerular filtration rate (GFR) (calculated with Modification of Diet in Renal Disease formula) was 8.0 ± 3.3 ml/min and mean value of kt/V was equal 1.2 ± 0.3 . In all patients hemodialysis was performed, using polysulfone dialyzer (Fresenius, Germany), three times per week and duration of each session was from 3.0 to 4.5 hours.

Concentration of the following cytokines was measured in a blood, immediately before start of hemodialysis session and at the end of treatment: HGF, IL-6, VEGF and MCP-1. All these cytokines were measured with the commercially available kits:

HGF: ELISA kit with detection limit 5.0 pg/ml (R&D, United Kingdom); IL-6: DuoSet ELISA kit with detection limit 0.7 pg/ml (R&D, United Kingdom); VEGF: ELISA kit with detection limit 5.0 pg/ml (R&D, United Kingdom). MCP-1: DuoSet ELISA kit with detection limit 5.0 pg/ml (R&D, United Kingdom).

Before start of the hemodialysis session all patients answered a short questionnaire composed of questions from KDQoL-SF [12]. The following questions were asked:

I. How do you evaluate your health status? 5 points scale from poor (1) to excellent (5).

II. How significant are limitations of your physical activity? The following items are about activities you might do during a typical day. Does your health now limit you in these activities (ie.vigorous activities such as running, lifting heavy objects; moderate activities such a moving a table, bowling; lifting or carrying groceries; climbing several or one flight of stairs; bending, kneeling; walking more than 1 mile, 500 meters, 100 meters; bathing or dressing yourself).

III. Does kidney disease interferes with your life? How true or false is each of the statements for you: my kidney disease interferes too much with my life; too much of my time is spent dealing with my kidney disease; I feel frustrated dealing with my kidney disease; I feel like a burden on my family.

IV. Did you feel any social/mental problems during last four weeks? Questions about how you feel and how things have been going during the past 4 weeks (did you isolate from people around you; did you react slowly to things that were said or done; did you act irritable toward those around you; did you have difficulty concentrating or thinking; did you get along well with other people; did you become confused;).

V. How frequent were kidney disease related disorders during last four weeks? During the past 4 weeks, to what extent were you bothered by each of the following: soreness in your muscles; chest pain; cramps; itchy skin; dry skin; shortness of breath; faintness or dizziness; lack of appetite; washed out or drained; numbness in hands or feet; nausea or upset stomach; problems with your access site.

VI. Does your disease affect your life activities? How does kidney disease bother you in each of the following areas: fluid restriction; dietary restriction; your ability to work around the house; your ability to travel; being dependent on doctors and other medical staff; stress or worries caused by kidney disease; your sex life; your personal appearance.

HGF and quality of life in hemodialysis patients

Table 1. Mean \pm SD values of serum concentration of Hepatocyte Growth Factor (HGF), Interleukin 6 (IL-6), Vascular Endothelial Growth Factor (VEGF) and Monocyte Chemoattractant Protein-1 (MCP-1) obtained before start of hemodialysis (START) and immediately after treatment (END)

	START	END	Δ END-Start
HGF [pg/ml]	378.6 \pm 182.2 range: 153.4-1011.3	822.4 \pm 337.2 range: 316.2-1959.2 P < 0.0001	443.8 \pm 322.7 range: -14.2-1510.1
IL-6 [pg/ml]	2.4 \pm 0.8 range: 1.4-4.1	2.8 \pm 0.9 range: 1.4-5.0 P < 0.01	0.3 \pm 0.6 range: -1.4-1.6
VEGF [pg/ml]	141.9 \pm 159.9 range: 10.6-952.3	163.7 \pm 159.4 range: 33.4-990.3 n.s.	21.8 \pm 63.1 range: -91.1-231.2
MCP-1 [pg/ml]	132.3 \pm 41.5 range: 40.2-265.4	154.2 \pm 82.5 range: 75.1-283.4	31.3 \pm 83.1 range: -81.5-195.2

Statistical analysis

Results are expressed as mean \pm SD. Statistical analysis was performed with Wilcoxon test for paired data. The relationship between HRQoL domains and analysed parameters was performed by multiple regression with forward selection. A *p* value less than 0.05 was considered statistically significant.

Results

One session of hemodialysis induced significant increase of serum concentrations of HGF (by 117%, *P* < 0.001), IL-6 (by 17%, *P* < 0.01). No significant change of serum VEGF and MCP1 concentration was observed (**Table 1**).

Patients evaluated their health status better than fair (2.3 \pm 0.8 in a scale from 1 = poor to 5 = excellent). Declared by the patient health status correlated with their age, GFR, kt/V, and hemodialysis induced change in serum IL-6 and HGF concentration (*R*² = 0.469, *P* < 0.001); details in **Table 2**.

Declared by the patients limitations of the physical activity correlated with their age, IL-6 serum concentration and hemodialysis induced change in serum HGF and VEGF concentration (*R*² = 0.362, *P* < 0.001); details in **Table 2**.

Patients declared that kidney disease interferes with their life (*R*² = 0.211, *P* < 0.001) and

that feeling correlated with their age, hemodialysis induced change in serum HGF and VEGF concentrations; details in **Table 2**.

Majority of patients declared that they had social/mental problems during previous four weeks (*R*² = 0.333, *P* < 0.001) and such opinions correlated with their age, and hemodialysis induced change in HGF and VEGF serum level; details in **Table 2**.

Patients reported that during previous 4 weeks they noticed physical disorders,

which could be related to their renal disease (*R*² = 0.163, *P* < 0.001) and such observations correlated with the hemodialysis induced change in HGF and IL6 serum level; details in **Table 2**.

Majority of patients reported that their kidney disease affects their life activities (*R*² = 0.422, *P* < 0.001) and such opinion correlated with their age, VEGF serum concentration and hemodialysis induced change in HGF and IL6 serum level; details in **Table 2**.

Discussion

Uremia causes deterioration of the quality of the life and that process is multifactorial. Age of the patients was an important factor determining poor subjective quality of life and limitation of the patients physical activity. Results of our study also confirm previous observations that intensity of the systemic inflammatory response correlates with the impaired quality of life [8-10]. We found that IL-6 serum concentration correlated with impaired physical activity in ESRD patients treated with hemodialysis (**Table 2**). The new finding in our study was significant correlation between hemodialysis induced inflammation and the patients quality of life.

Our results confirm that even one session of hemodialysis enhances the systemic inflammation, what was also shown in other studies [13, 14]. However we must stress that there was a wide variation in the character and intensity of the hemodialysis-induced inflammatory

HGF and quality of life in hemodialysis patients

Table 2. Presentation of the factors which are related with the patients opinions about their daily problems related to the end stage renal failure requiring hemodialysis

Question	Parameter	$\beta 2$	Statistical significance
How do you evaluate your health status?	Age	-0.278	P < 0.005
	GFR	0.332	P < 0.0005
	Kt/V	0.266	P < 0.005
	Δ HGF	0.353	P < 0.0001
	Δ IL6	-0.260	P < 0.05
How significant are limitations of your physical activity?	Age	0.313	P < 0.002
	IL6	0.250	P < 0.01
	Δ HGF	-0.389	P < 0.0001
	Δ VEGF	0.274	P < 0.005
Does kidney disease interferes with your life?	Age	0.276	P < 0.01
	Δ HGF	-0.353	P < 0.001
	Δ VEGF	0.261	P < 0.01
Did you feel any social/mental problems during last four weeks?	Age	0.310	P < 0.002
	Δ HGF	-0.287	P < 0.005
	Δ VEGF	0.335	P < 0.002
How frequent were kidney disease related disorders during last four weeks?	Δ HGF	-0.335	P < 0.005
	Δ IL6	0.240	P < 0.05
How does your kidney disease affects your life activities?	Age	0.209	P < 0.05
	VEGF	-0.261	P < 0.005
	Δ HGF	-0.408	P < 0.001
	Δ IL6	0.380	P < 0.001

response in our studied group (**Table 1**). Such effect may be due to dysfunction of the immune system during uremia [15], what may result in dysregulation of the balance between proinflammatory and anti-inflammatory factors [16]. Hemodialysis may enhance that disproportion. We found correlation between hemodialysis induced rise of IL-6 or VEGF and various aspects of the impaired physical or psychological quality of life in the studied group of the renal patients. Opposite observations were done for HGF. In general stronger increase of HGF concentration in serum correlated with better quality of life in the studied group of patients. Contrary to IL-6 or VEGF, which can be considered as the proinflammatory cytokines, HGF has rather antiinflammatory, antifibrotic properties.

In our study, one session of hemodialysis induced increase of serum HGF concentration in majority of patients (74 out of 76), however that effect was not uniform in all patients (**Table 1**). Increase of serum HGF could be due to application of heparin [17], but we cannot

exclude that process of hemodialysis itself causes such change, due to stimulation of peripheral blood mononuclear cells [18]. Libetta et al. described hemodialysis-induced rise in serum HGF concentration which is however short lasting and during the hemodialysis session serum level of that cytokine gradually decreases [18]. Rampino and coworkers demonstrated however that during hemodialysis, performed without heparin, increased serum level of HGF remains for 240 minutes and peripheral blood mononuclear cells harvested at the end of session released more HGF than at the start [19]. We found that only in 1 patient out of 76 serum HGF concentration was lower at the end of the hemodialysis session as compared to the predialysis value. In our study there was

a wide range of initial, predialysis HGF level in serum (153-1011 ng/ml) but there was no correlation between these values and change of its concentration during hemodialysis session. There was also no correlation between predialysis HGF levels and any of the studied parameters reflecting the quality of life in the studied patients. We found however that patients with smaller increase of HGF during hemodialysis session reported not only more limitations of the physical activity, and disorders related to renal failure, but also impaired coping with life during last weeks and stronger interference of the renal disease with their life (**Table 2**). To summarize, our results suggest that lowhemodialysis-induced increase of serum HGF correlates with reduced quality of life in patients with end stage renal failure and on the replacement therapy.

We must stress however that not all observations, despite the statistically significant correlation, were really strong (**Table 2**), what can be considered a weak part of our study. The explanation for such situation may be the fact that

number of patients participating in the study was not large, there was a wide variation of the patients age (32-84 years), various time of treatment with dialysis (5 months-42 months) and wide range of GFR (3-14 ml/min). We eliminated from the studied group patients with diabetes mellitus, neoplastic disease, liver disease or acute inflammatory disorders, what made our group more homogenous. However we believe that each patient has an individual reaction to the stress induced by hemodialysis, what is due not only due to pathological but also physiological properties of the body.

Hepatocyte Growth Factor despite its name is the molecule with the highest expression in the kidney and regulates many processes in that organ [20]. It has the cytoprotective effect in acute renal failure and higher serum levels of HGF correlate with faster recovery of the renal function [18]. HGF concentration is increased in patients with chronic renal failure and it results in preservation of the renal structure and function due to its various effects, such as inhibition of the renal fibrosis [21] or by modulation of the renal inflammation [22]. It was suggested that increased HGF level counteracts the effect of the inflammatory cytokines which stimulate progression of the renal damage [23]. In fact, *in vivo* gene transfer of HGF prevents progression of the renal failure [24]. There is also evidence that HGF has an anti-inflammatory effect on the level of the inflamed endothelium [25]. We suggest that hemodialysis-induced increased HGF serum level counteracts the systemic inflammation, progression of the renal damage, what translates into better quality of life in patients with end-stage renal failure. Previously Rampino et al. reported that in patients with end stage renal failure and hepatitis C liver disease was more benign and they linked that observation with the hemodialysis induced rise of serum concentration of HGF [26]. One can expect that repeated stimulation of HGF release/synthesis by process of hemodialysis in patients with chronic renal failure may result in protective effect of that cytokine in the kidney, slowing deterioration of its function as it was observed in patients with acute renal failure [18]. However we found that magnitude of change of serum HGF concentration at the end of the dialysis session varies in the individual patients (from decrease by 14 ng/ml to rise by 1510 ng/ml). Supplementation with HGF should be therefore considered in patients with reduced intravascular stimulation of HGF synthesis/release [27]. One can specu-

late that addition of the exogenous HGF, or stimulation of its synthesis, in that group of patients may result in improved quality of life, secondary to amelioration of the renal function and reduction of the systemic uremic complications. Supplementation with exogenous HGF appeared to be effective in various types of experimental studies [28, 29]. Further studies are required to verify that hypothesis.

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Disclosure of conflict of interest

None.

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HGF and quality of life in hemodialysis patients

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