# HA130 AND UREMIC PRURITUS IN DIALYSIS PATIENTS

**Uremic Pruritus/Itching** is a common problem for patients with chronic renal failure or end stage renal disease.

Most affected sites: back, abdomen, head and /or arms.

## Clinical Presentation

- Skin changes due to intense scratching activity (Fig. 1)[1].
- 84% of patients have itching daily[2].
- Affect large discontinuous but bilateral and symmetric skin areas[2].
- Itching gets worsening at night[2].

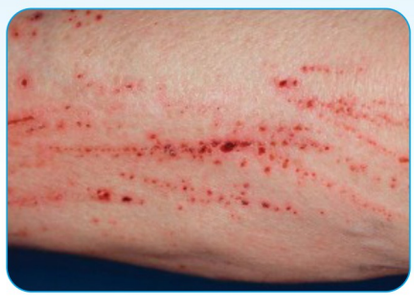

Fig. 1 Skin changes in uremic pruritis[1]

## Prevalence of Uremic Pruritus

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in a very large cohort of patients on hemodialysis in different countries revealed that ~ 45% of patients suffered from CKD-associated itch (Fig. 2)[3].

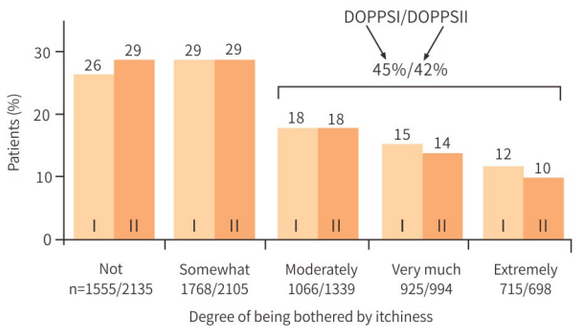


Fig. 2 Prevalence and intensity of uremic pruritus according to DOPPS-data from 1996 to 1999 (I) and 2002 to 2003(Ⅱ)[3].

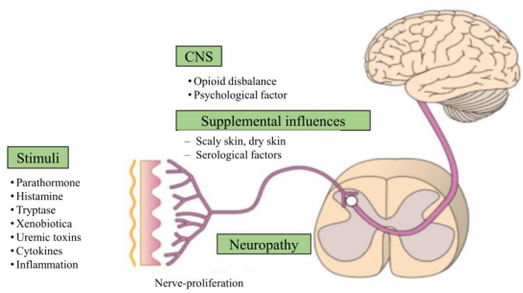


Fig. 3 Schematic synopsis of potential pathogenic factors in chronic kidney disease-associated pruritus[1].

## Pathogenesis

- Parathyroid hormone (PTH) and histamine as well as calcium and magnesium salts have been reported as pathogenetic factors (Fig. 3)[1].
- Systemic inflammation: derangements of the immune system with a proinflammatory pattern may be involved in the pathogenesis of CKD associated itch (Fig. 3)[1].
- Studies revealed that pruritus patients had higher levels of C-Reactive Protein (CRP)[1].

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# BENEFITS OF HA130 IN UREMIC PRURITUS

HA130 disposable hemoperfusion cartridge with a very large adsorption surface (~20,000m$^2$) is considered a new solution for uremic pruritus patients when combined with conventional haemodialysis by:

- Reducing the PTH (Fig. 4)[4].
- Reducing the inflammatory mediators and markers such as IL-6 and hsCRP (Fig. 5,6)[5].
- Decreasing the pruritus score (Fig. 7)[6].
- Relieving patients' itching signs and symptoms[4-6].

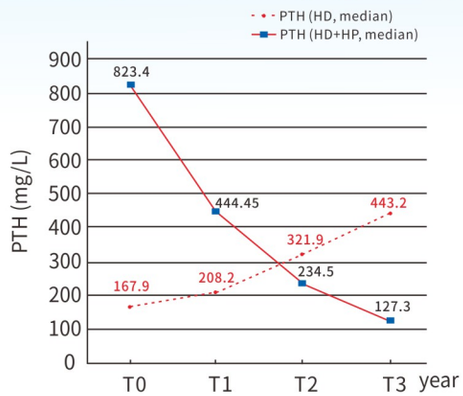


Fig. 4 PTH levels changes[4]

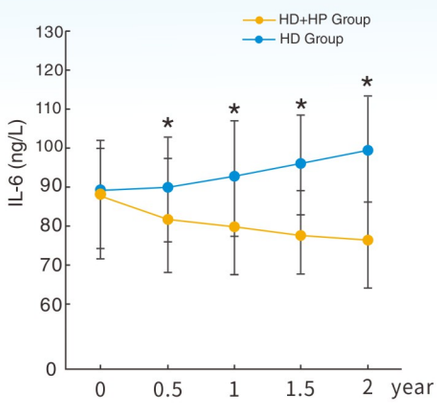


Fig. 5 IL-6 levels changes, *p<0.05[5]

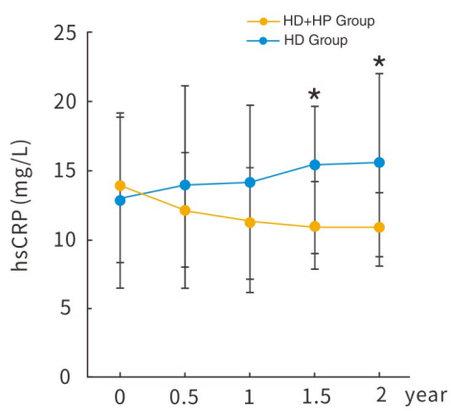


Fig. 6 hsCRP levels changes, *p<0.05[5]

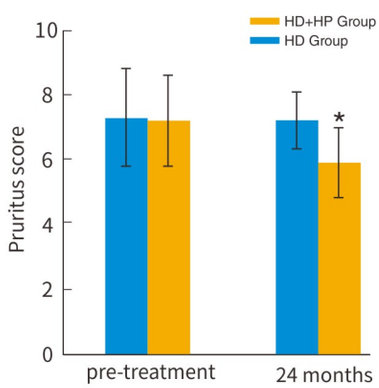


Fig. 7 Pruritus score changes, *p<0.01[6]

- PTH Controller
- Inflammation Regulator
- Uremic Pruritus Alleviator

[1] Mettang, Thomas, and Andreas E. Kremer. "Uremic pruritus." Kidney international 87.4 (2015): 685-691.
[2] Mathur, Vandana S., et al. "A longitudinal study of uremic pruritus in hemodialysis patients." Clinical Journal of the American Society of Nephrology 5.8 (2010): 1410-1419.
[3] Pisoni, Ronald L., et al. "Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)." Nephrology Dialysis Transplantation 21.12 (2006): 3495-3505.
[4] Huu, Dung Nguyen, et al. "A Combination of Hemodialysis with Hemoperfusion Helped to Reduce the Cardiovascular-Related Mortality Rate after a 3-Year Follow-Up: A Pilot Study in Vietnam." Blood purification 50.1 (2021): 65-72.
[5] Chen, Shun-Jie, et al. "Combination of maintenance hemodialysis with hemoperfusion: a safe and effective model of artificial kidney." The International journal of artificial organs 34.4 (2011): 339-347.
[6] Gu, Yan Hong, et al. "Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis." The International journal of artificial organs 42.7 (2019): 347-353.

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CY-HA130LCDYSY-01-08-2021-EN

# HA130 AND DIALYSIS RELATED AMYLOIDOSIS

**Dialysis-Related Amyloidosis (DRA)** is a serious complication of long-term dialysis therapy and is characterized by the deposition of $\beta_2$- microglobulins ($\beta_2$-MG) in the osteoarticular structures and viscera.

DRA mainly involves the osteoarticular system (bone, synovium, muscle, tendon and ligaments). The frequently involved articulations are arm joints, such as scapulohumeral and the carpal bones (Fig. 1), and the cervical neck.

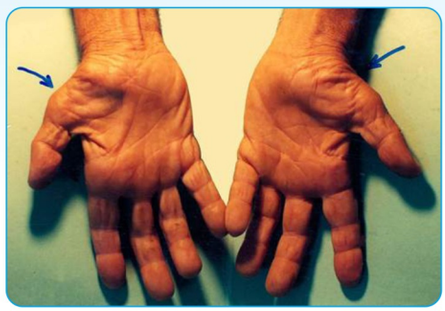

Fig. 1 Thumb muscle atrophy from untreated CTS (wikipedia)

## Prevalence of DRA

DRA can be seen in as much as 20% of patients after 2–4 years of hemodialysis (HD) and in 100% of patients after 13 years of HD[1].

## Prognosis of DRA

- Carpal tunnel syndrome (CTS)
- Bone cysts
- Scapula–humeral periarthritis
- Joint arthropathy
- Destructive spondyloarthropathy

## Pathogenesis

- Deposition of amyloid fibrils principally composed of $\beta_2$-MG caused by long-term dialysis therapy (Fig. 2)[2].
- The released cytokines, including interleukin (IL)-1, tumor necrosis factor-α (TNF-α ), and IL-6 are thought to stimulate the synthesis and release of $\beta_2$-MG and this inflammatory component of amyloid deposits contributes to the development of the destructive lesions of bones and joints in DRA patients[3].

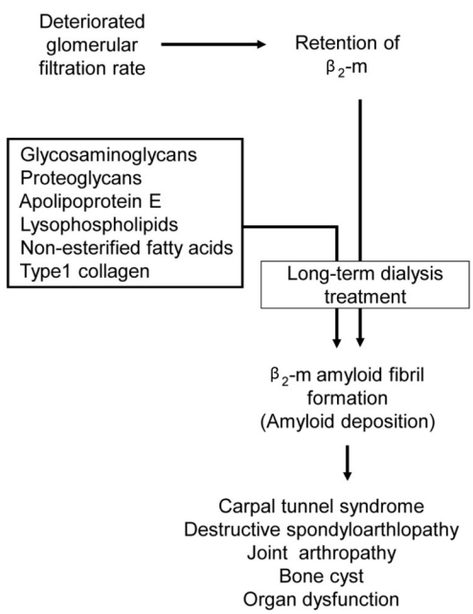


Fig. 2 Pathogenesis of DRA[2]

AMYLOIDOSIS

# BENEFITS OF HA130 IN DRA

HA130 disposable hemoperfusion cartridge with high adsorption capacity when combined with conventional hemodialysis could benefit DRA patients by :

- Decreasing the levels of $\beta_2$-MG (Fig. 3)[4,5].
- Reducing inflammatory mediators related to DRA such as TNF-α (Fig. 4) and IL-6[5].
- Preventing and slowing the progression of DRA such as slowing and preventing the progression of CTS (Table. 1)[4,5].
- Relieving the symptoms and signs of DRA such as pain of shoulders and bone (Table. 1)[4,5].

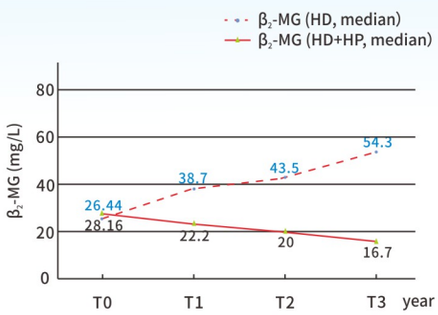


Fig. 3 Changes of serum $\beta_2$-MG[4]

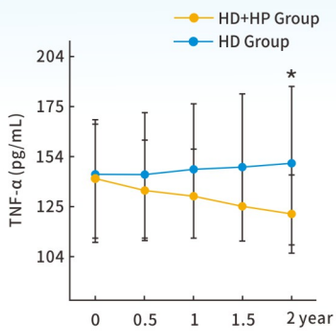


Fig. 4 Changes of serum TNF-α, * P<0.05[5]

## Table. 1 Comparison of clinical characteristics between the two groups after 3 years[4]

| | HD+HP (1) | | HD (2) | | *p* values |
|---|---|---|---|---|---|
| | T0 (n=44) | T3 (n=44) | T0 (n=39) | T3 (n=39) | |
| Pain of shoulder and bone | | | | | |
| n(%) | 15 (44) | 6 (13.63) | 10 (25.64) | 18 (46.15) | pT3 (1-2):0.003 |
| *p* values | | 0.023 | | 0.057 | |
| Capral tunnel syndrome | | | | | |
| n(%) | 11 (25) | 9 (20.45) | 10 (25.64) | 12 (30.76) | pT3 (1-2):0.475 |
| *p* values | | 0.607 | | 0.613 | |

T0, T3: Before and after 36 months of starting treatment

- $\beta_2$-MG & DRA Inflammatory Factors Controller
- DRA Progression Protector

[1] Jadoul M, Garbar C, Noël H, et al. Histological prevalence of beta 2-microglobulin amyloidosis in hemodialysis: a prospective postmortem study. Kidney Int. 1997; 51(6):1928–1932.
[2] Yamamoto, Suguru, et al. "Dialysis-related amyloidosis: Pathogenesis and clinical features in patients undergoing dialysis treatment." Japan: INTECH (2013): 67-83.
[3] Schaeffer J, Floege J, Ehlerding G, Koch KM. Pathogenetic and diagnostic aspects of dialysis-related amyloidosis. Nephrol Dial Transplant. 1995;10 (Suppl 3):S4–S8.
[4] Huu, Dung Nguyen, et al. "A Combination of Hemodialysis with Hemoperfusion Helped to Reduce the Cardiovascular-Related Mortality Rate after a 3-Year Follow-Up: A Pilot Study in Vietnam." Blood purification: 1-8.
[5] Chen, Shun-Jie, et al. "Combination of maintenance hemodialysis with hemoperfusion: a safe and effective model of artificial kidney." The International journal of artificial organs 34.4 (2011): 339-347.

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CY-HA130LCDYDFYB-01-08-2021-EN

# IMPACT OF HA130 ON QUALITY OF LIFE AND SURVIVAL RATE IN DIALYSIS PATIENTS

**Quality of Life (QoL)** impairment in patients with end stage renal disease is mainly caused by the accompanied deterioration or by the imposed limitations in almost all domains of their daily lives.

The mean overall score of health-related QoL and all subscales of patients using a standard short-form questionnaire of short form-36 was significantly lower than controls[1]. Variables related to physical activity and depression seem to have a direct impact on Quality of life (QoL) and Health-Related Quality of Life (HRQoL). Others, such as anxiety, awareness, empowerment, the presence of sleep disorders, satisfaction, support from the staff, social support, spirituality and religion have a clear correlation with the QoL dimension (Fig. 1)[2,3].

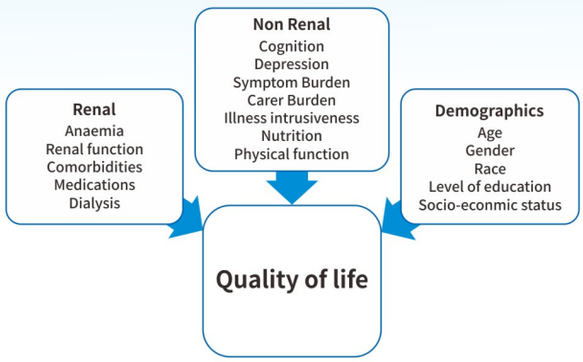


Fig. 1 Determinants of quality of life in advanced kidney disease[2].

## Prevalence of Kidney Failure

Internationally the numbers are staggering. Estimates are that 2 million people worldwide suffer from kidney failure, and the number of patients diagnosed with the disease continues to increase at a rate of 5-7% per year[4].

## Mortality Rate

Mortality rates vary depending on the kidney failure treatment. After one year of treatment, those on dialysis have a 20-25% mortality rate, with a 5-year mortality rate of 65% (Fig. 2)[5,6].

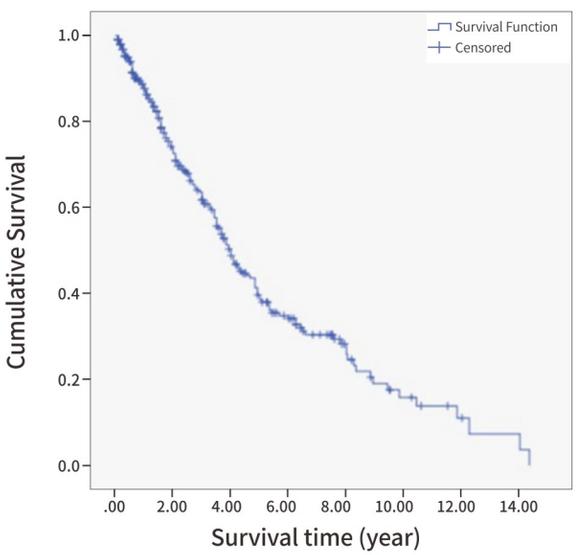


Fig. 2 Kaplan–Meier survival curves of chronic hemodialysis[6].

QUALITY OF LIFE

# BENEFITS OF HA130 IN QUALITY OF LIFE AND SURVIVAL RATE

## Improve Quality of Life

The findings of HA130+HD treatment suggested a potential role in improving the quality of life by improving pruritus, body pain, general health, vitality and total QoL score etc. (Fig. 3)[7-9].

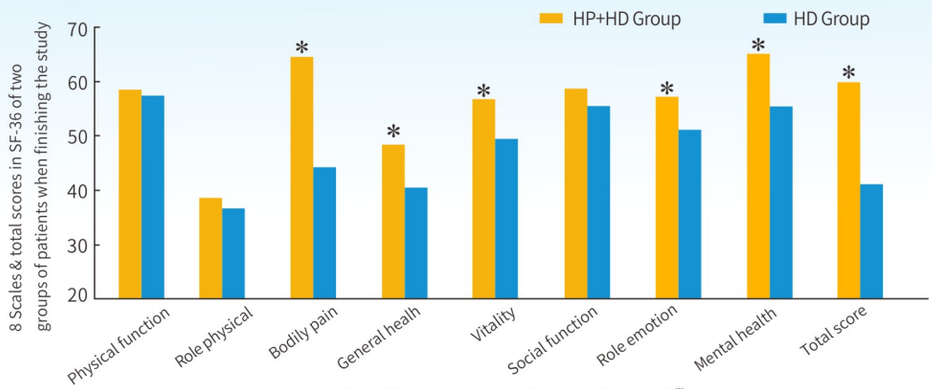


Fig. 3 SF-36 scores for HA130+HD vs HD, *p<0.05[7]

## Improve Survival Rate

Previous studies showed significant benefits in reducing the cardiovascular events and improving survival rate in HA130+HD group compared to conventional dialysis (Fig. 4)[8, 9].

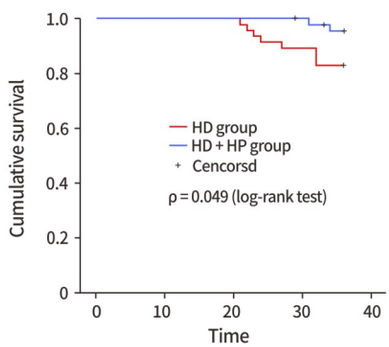


Fig. 4 survival curve after 36 months of observation, p = 0.049[9]

- Reduce Uremic Toxins
- Improve Quality of Life
- Reduce Cardiovascular Events
- Reduce Overall Mortality Rate

QUALITY OF LIFE

[1] Hajian-Tilaki, K., B. Heidari, and A. Hajian-Tilaki. "A comparison of health-related quality of life in patients with renal failure under hemodialysis and healthy participants." Saudi Journal of Kidney Diseases and Transplantation 28.1 (2017): 133.
[2] Iyasere, Osasuyi, and Edwina A. Brown. "Determinants of quality of life in advanced kidney disease: time to screen?." Postgraduate medical journal 90.1064 (2014): 340-347.
[3] Cangini, G., et al. "Evolution of the concept of quality of life in the population in end stage renal disease. A systematic review of the literature." La Clinica Terapeutica 170.4 (2019): e301-e320.
[4] University of California San Francisco. 2018. “The Kidney Project.” https://pharm.ucsf.edu/kidney/need/statistics
[5] https://pharm.ucsf.edu/kidney/need/statistics
[6] Nguyen, Bach, and Fumiko Fukuuchi. "Survival rates and causes of death in Vietnamese chronic hemodialysis patients." Renal Replacement Therapy 3.1 (2017): 22.
[7] Chen, Shun-Jie, et al. "Combination of maintenance hemodialysis with hemoperfusion: a safe and effective model of artificial kidney." The International journal of artificial organs 34.4 (2011): 339-347.
[8] Gu, Yan Hong, et al. "Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis." The International journal of artificial organs 42.7 (2019): 347-353.
[9] Huu, Dung Nguyen, et al. "A Combination of Hemodialysis with Hemoperfusion Helped to Reduce the Cardiovascular-Related Mortality Rate after a 3-Year Follow-Up: A Pilot Study in Vietnam." Blood purification: 1-8.

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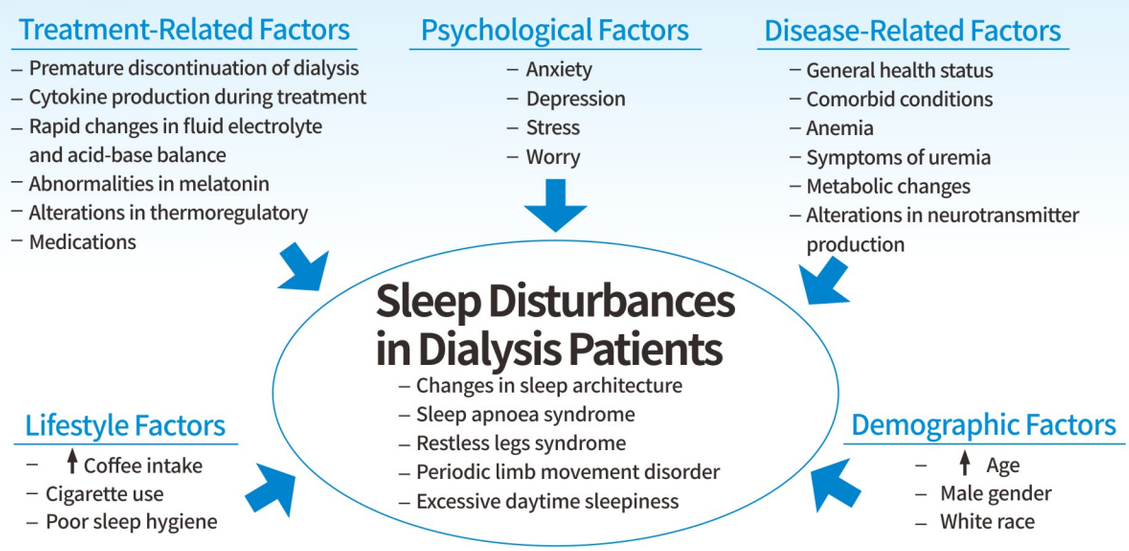
CY-HA130LCDYSHZL-01-08-2021-EN

# HA130 AND SLEEP DISTURBANCES IN DIALYSIS PATIENTS

**Sleep disturbances** are extremely common among dialysis patients. Sleep complaints are reported in up to 80% of CKD patients[1,2].



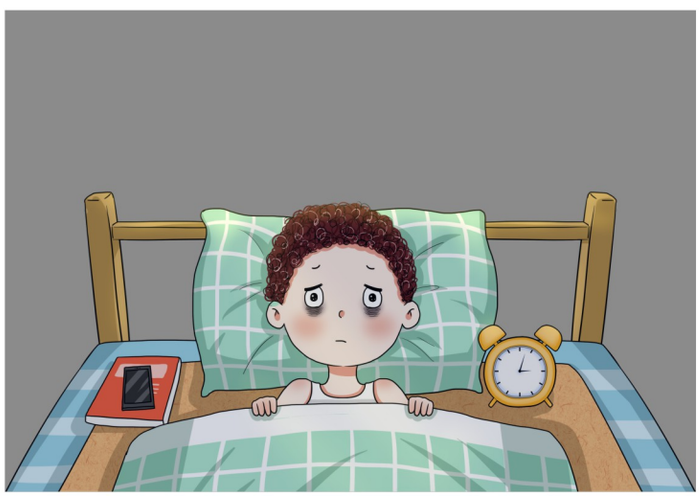

Overview of possible mechanisms of leading to sleep disturbances in CKD[3]

## Common Causes

- Presence of pain[4]
- Absence of melatonin surge[5]
- Congestive heart failure[4]
- Psychiatric disorders[4]
- Depression[4]
- Pruritus[4]
- Lower QoL scores[4]
- Socioeconomic status[4]

## Common Complaints

- Falling asleep (daytime)
- Nighttime awaking
- Early morning awaking
- Restless legs
- Jerking legs



SLEEP DISTURBANCES

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SLEEP DISTURBANCES

# BENEFITS OF HA130 ON DIALYSIS RELATED SLEEP DISTURBANCES

HA130 disposable hemoperfusion cartridge could adsorb the middle molecule and protein-bound uremic toxins, it can benefit the dialysis related sleep disturbances by:

- Reducing PTH levels which result in relieving the pruritis (Fig. 1)[6-8].
- Decreasing $\beta_2$-MG which lead to improve the DRA and the body pain[6,7].
- Reducing the inflammatory mediators which associated with sleep disturbances[8].
- Regulating the melatonin levels which play a major role in circadian sleep-wake rhythm (Fig. 2)[7].
- Improving the quality of life score[6,8].
- Increasing the sleep duration and sleep efficacy (Table. 1)[7].

Table. 1 Comparison of sleep related markers between the two groups[7]

| | Baseline | | p | End of treatment | | p |
|---|---|---|---|---|---|---|
| | HD | HD+HP | | HD | HD+HP | |
| **Sleep parameters** | | | | | | |
| Sleep duration (min) | 360±16.6 | 370±15.1 | NS | 368±25.2 | 418±22.7 | <0.05 |
| Sleep efficiency (%) | 76±5.5 | 78±6.9 | NS | 78.5±5.4 | 88.2±3.5 | <0.01 |

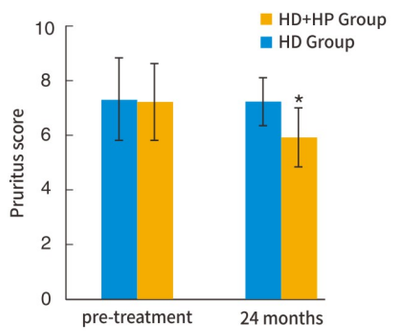

Fig. 1 Changes of pruritis score, *p < 0.05[13]

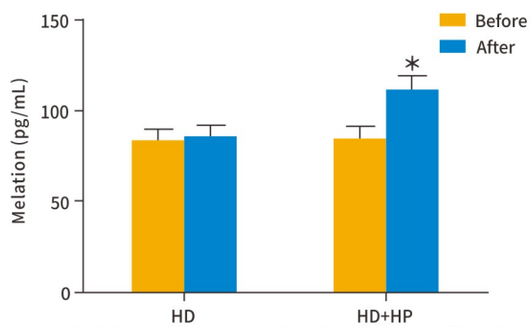

Fig. 2 Comparing nocturnal melatonin value between HD and HD+HP groups before and after 24-month follow-up period[7]

- Complication Controller
- Sleep Protector
- Melatonin Regulator


[1] Merlino G. Piani A. Dolso P. Adorati M. Cancelli I. Valente M. Gigli G. L. 2006 Sleep disorders in patients with end stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant; 21 184
[2] Iliescu E. A. Coo H. Mc Murray M. H. Meers C. L. MM Quinn MA Singer Hopman W. M. 2003 Quality of sleep and health-related quality of life in haemodialysis patients. Nephrol Dial Transplant 18 126 132
[3] Parker KP. Sleep disturbances in dialysis patients. Sleep Med Rev. 2003;7:131-143.
[4] Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2008; 23:998–1004. [PubMed: 17911092]
[5] Koch BC, Nagtegaal JE, Kerkhof GA, ter Wee PM. Circadian sleep-wake rhythm disturbances in end-stage renal disease. Nat Rev Nephrol. 2009; 5:407–416. [PubMed: 19468289]
[6] Huu, Dung Nguyen, et al. "A Combination of Hemodialysis with Hemoperfusion Helped to Reduce the Cardiovascular-Related Mortality Rate after a 3-Year Follow-Up: A Pilot Study in Vietnam." Blood purification: 1-8.
[7] Gu, Yan Hong, et al. "Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis." The International journal of artificial organs 42.7 (2019): 347-353.
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CY-HA130LCDYSMZA-01-08-2021-EN

# HA130 AND REFRACTORY HYPERTENSION IN DIALYSIS PATIENTS

**Resistant/Refractory Hypertension** is uncontrolled despite use of ⩾3 anti-hypertensive medications (Fig. 1).

- Hypertension is present in more than 80% of ESRD cases[2].
- 50-70% of hypertensive patients in chronic hemodialysis programs are not efficiently controlled[5].
- The targeted blood pressure (BP) values of < 140/90 mmHg are recommended in order to reduce cardiovascular morbidity and mortality in dialysis patients[3].

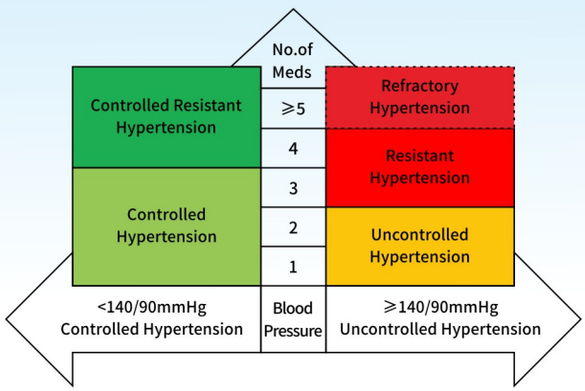


Fig. 1 Classification of HTN as per number of drugs[1]

## Pathogenesis

Elevated blood pressure in ESRD patients who receive dialysis is common and poorly controlled in general. Although volume overload and sodium retention appear to be the main pathogenic mechanism of hypertension in this population, other factors such as increased arterial stiffness, activation of renin-angiotensin-aldosterone system, sleep apnea, activation of sympathetic nervous system, and use of recombinant erythropoietin may be also involved (Fig. 2)[4,5].

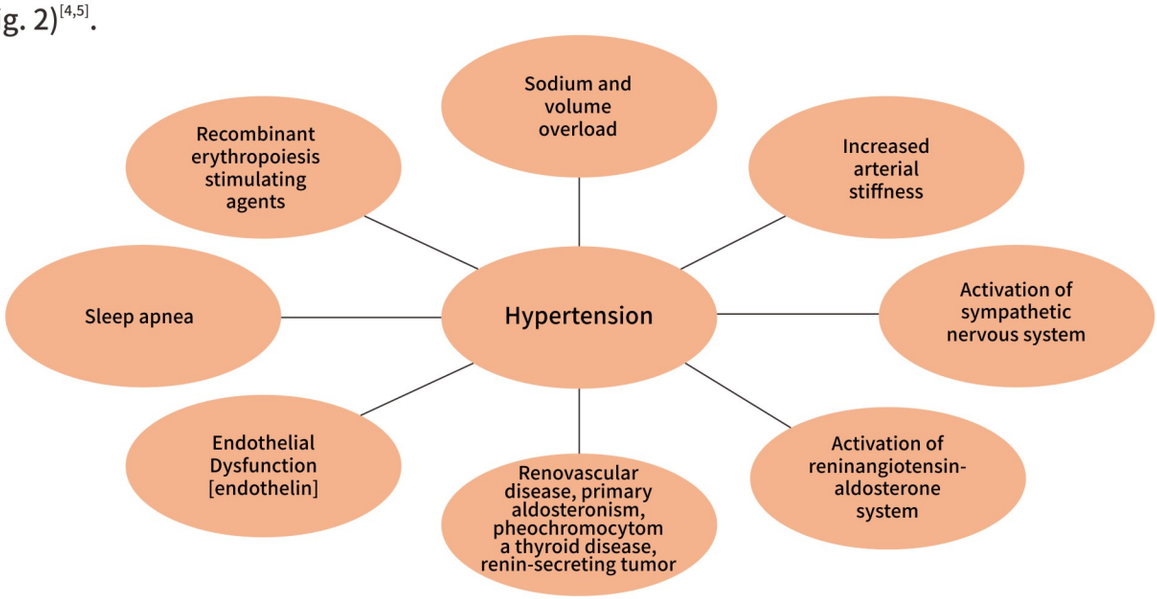


Fig. 2 Factors involved in the development of hypertension in dialysis patients[5].

# BENEFITS OF HA130 ON REFRACTORY HYPERTENSION

The adsorption of middle uremic toxin and protein-bound toxins using HA130 combined with haemodialysis could benefit the dialysis patients with refractory hypertension by:

- Controlling the Renin- Angiotensin II- Aldosterone levels (Table. 1)[6].
- Improving sleep apnea[7].
- Reducing the Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) (Table. 1), (Fig. 3)[6,8].
- Minimizing the use of antihypertensive agents (Table. 1)[6].
- Reducing the cardiovascular related events[9,10].

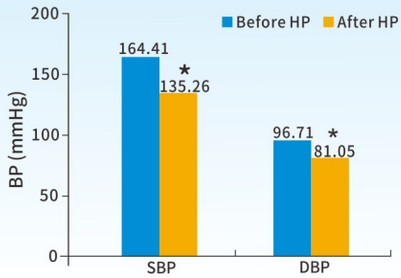


Fig. 3 Comparison of BP before and after HP treatment , *p<0.05[8]

Table. 1 Comparison of outcomes between control and observation group[6]

| | Group | RA (ng/ml) | AngⅡ (pg/ml) | Aldosterone (pg/ml) | SBP (mmHg) | DBP (mmHg) | Hypotensor |
|---|---|---|---|---|---|---|---|
| 0M | Control Group (n=30) | 2.22±0.61 | 834.85±219.50 | 497.55±217.06 | 175.10±8.67 | 98.50±7.77 | 4(3, 5) |
| | Observation Group(n=45) | 2.20±0.62 | 856.72±305.33 | 491.37±256.88 | 176.38±10.07 | 98.51±6.75 | 4(3, 5) |
| | T value | 0.138 | −0.338 | 0.108 | −0.569 | −0.007 | |
| | P value | 0.891 | 0.736 | 0.914 | 0.571 | 0.995 | 0.394 |
| 3M | Control Group (n=30) | 2.26±0.52 | 805.56±218.20 | 460.10±161.48 | 172.83±7.90 | 98.57±5.52 | 4(3, 5) |
| | Observation Group(n=45) | 2.21±0.58 | 829.09±262.03 | 477.57±209.17 | 175.40±8.04 | 97.29±6.14 | 4(2, 5)1) |
| | T value | 0.398 | −0.407 | −0.387 | −1.364 | 0.919 | |
| | P value | 0.692 | 0.686 | 0.700 | 0.177 | 0.361 | 0.301 |
| 6M | Control Group (n=30) | 2.15±0.49 | 850.98±158.76 | 489.91±155.50 | 168.03±7.77 | 95.60±17.59 | 3.5(2, 5) |
| | Observation Group(n=45) | 1.29±0.43 | 747.26±209.76 | 421.59±168.16 | 153.04±7.16 | 87.64±5.01 | 2(0, 4)1) |
| | T value | 8.118 | 2.302 | 1.776 | 8.579 | 2.872 | |
| | P value | 0.000 | 0.024 | 0.080 | 0.000 | 0.005 | 0.000 |
| 12M | Control Group (n=30) | 2.14±0.48 | 851.06±157.66 | 490.98±159.84 | 169.40±7.53 | 96.37±17.57 | 4(2, 5) |
| | Observation Group(n=45) | 1.27±0.41 | 736.10±199.64 | 412.61±156.45 | 152.93±7.08 | 87.73±5.60 | 2(0, 4)1) |
| | T value | 8.462 | 2.649 | 2.107 | 9.620 | 3.079 | |
| | P value | 0.000 | 0.010 | 0.039 | 0.000 | 0.003 | 0.000 |

- Blood pressure Controller
- Cardiovascular Protector
- RAAS Regulator

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*Contraindications or warnings refer to Instructions For Use

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