HAEMODIALYSIS PRODUCT : A RELIABLE NEW INDEX FOR DIALYSIS ADEQUACY

Thesis

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Abbreviations

LMWP	low MW peptides
DHD	Daily hemodialysis
DOPPS	Dialysis outcomes and practice patterns study
AGE	Advanced glycated end products
APR	Acute phase reactants
BMI	Body mass index
Bun	Blood urea nitrogen
Bun – Post	Postdialysis Blood urea nitrogen
Bun-pre	Predialysis blood urea nitrogen
HEMO Study	Mortality and Morbidity in Hemodialysis
NECOSAD	Netherlands co-operative study on adequacy of dialysis
UKM	Urea kinetic modeling
CRF	Chronic renal failure
Da	Dalton
DOQI	Dialysis outcomes quality initiative
K- DOQI	Kidney diseases outcomes quality initiative
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HD	Hemodialysis
HDP	Hemodialysis product
Hr	Hour(s)
ID	Interdialytic
IGF-1	Insulin growth factor-1

IgG	Immunoglobulin G
Kg	Kilogram
KDa	Kilodalton
Kt/v	Dialyzer clearance of urea.
L	Litre
MAC	Mid-arm circumference.
MAMC	Mid-arm muscle circumference
MM	Middle molecules
MMOL	Millimol
MW	Molecular weight
CRP	C-reactive protein
nPcR	Normalized protein catabolic ratio
PcR	Protein catabolic rate
PNA	Protein equivalent of nitrogen appearance
Pre-alb	Pre-albumin
PTH	Parathyroid hormone
TACurea	Timed average urea concentration
Trans	Transferrin
TSF	Triceps skin fold thickness
vs.	Versus
Wt-Post	Post-dialysis weight
Wt-Pre	Predialysis weight
yr	Year

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INTRODUCTION AND AIM OF THE WORK

Introduction :

The great belief among the hemodialysis community in the reliability of Kt/V which combined with the natural desire of the patient to have the shortest possible time on dialysis, has resulted in underdialysis in majority of hemodialysis patients ***(Pastan and Bailey, 1988)***

Inadequate dialysis in US hemodialysis patients has resulted in high mortality rates at 23% per year. Inadequate dialysis is also associated with increased hospitalizations with high inpatient costs ***(Sehgal., 2002).***

These results has made Kt/v to be re-evaluated as an accurate parameter of uremic toxins removal ***(Vanholder 2002)***.

The additional evidence that Kt/v is an inaccurate parameter is that it prefers short hemodialysis which is inefficient in removing toxic middle molecules but gives a false impression of highly efficient hemodialysis by removing fast diffusing urea and thus, resulting in a high Kt/V ***(Pastan and bailey, 1998).***

So, the adequacy of hemodialysis depends more on the removal of middle molecules rather than the removal of urea ***(Charra and Laurent, 1999)***.

All of these made ***Scribner and Oreopoulos (2002)*** to propose a new index of adequacy of hemodialysis, to be called The Hemodialysis Product (HDP). This new index incorporates dialysis frequency, and duration of session:

HDP = (hrs/dialysis session) X (sessions/wk)^2

Aim of the work:

To evaluate hemodialysis product as a new index for adequacy of hemodialysis including nutritional status and performance of the patients and to compare it to (Kt/V) and urea reduction ratio (URR) as a parameters for adequacy of dialysis aiming to reach the optimum dialysis dose.

Chronic renal failure

C.R.F is a functional diagnosis characterized by a progressive and generally irreversible decline in glomerular filtration rate (GFR) ***(David, 1996)*** and increasing inability of the kidney to maintain normal low levels of the product of protein metabolism, normal blood pressure, hematocrit value, sodium, water, potassium and acid base balance ***(Remuzzi JI et al., 1997).***

CRF occurs when GFR is below 30 ml//min, symptoms and complications of uremia often occur when the GFR is less than 15ml/minute ***(Walls, 1995).***

Uremic toxins in CRF :

Uremic toxins are the compounds that accumulate in the blood and tissues in parallel with the progression of renal failure and induce a deterioration of biochemical, physiological and cellular functions resulting in a combination of complex and variable symptoms that characterize the uremic syndrome.

Bergstrom, J, (1995) proposed that a uremic toxin should satisfy the following criteria:

1- The chemical identity of the compound and its quantity in biologic fluids should be known.

2- Its concentration in tissue or plasma from uremic subjects should exceed that present in non uremic subjects.

3- Its concentration should correlate with specific uremic symptoms, and the symptom or symptoms should disappear when the concentration is reduced to normal.

4- Toxicity of the compound in tissue, cells or a test system should be demonstrated at the concentration found in tissue or fluids from uremic patients.

Classification of uremic toxins :

Low molecular weight solute (Mw<200 Da) :

Most small uremic toxins are nitrogenous in nature.

Urea (60 –Da) is the most recognized among them since it represents 80% or more of total nitrogen excreted into urine ***(Richet, 1988)***

Urea has generally been considered to be relatively non toxic at least at the concentrations currently encountered in uremia. ***(Bergstrom. J,1983)***, functioning more as surrogate for other unidentified low M.W. uremic toxins, ***(Sargent, JA, Gotch ,1995)***.

Brenner, Lazarus (1994) considers that uremic symptoms correlate only in a rough and inconsistent way with the concentration of urea in blood. Although not a major cause of uremic toxicity, urea account for some clinical abnormalities including anorexia, malaise, vomiting and headache.

Middle molecules (MM) and low MW peptides (LMWP) :

Classical MM range from (300-2000 Da), however several clinical metabolic and biochemical disturbances of the uremic syndrome are caused by compounds that do not always conform to that range. Retention of LMWP (MW < 12000 Da) has been widely recognized to play a role in uremic toxicity. Moreover smaller compounds with a MW < 300 Da may

behave like MM during hemodialysis (HD) due to their stearic configuration, electrostatic charge, protein binding and resistance of cell membranes towards gradient dependent solute transfer ,***(European Renal Association, 2002)***. The most accepted among them are as follows:

Beta 2 – microglobulin (β2-m) (11.8 KDa) :

Uremia-related amyloid as found in bone disease and carpal tunnel syndrome, is composed mainly of β2-m ***(Floege et al., 1996)***.

Myloid deposits may be detected as early after 1-2 years in the setting of HD ***(Garbar et al., 1997)***.

Advanced glycated end products (AGE):

Several AGE compounds are peptide-linked degradation products. AGE are retained in uremia, during which their concentration increases up to tenfold ***(Henle et al., 1999)***.

AGE are responsible for tissue damage and functional disturbances. AGE cause an inflammatory reaction in monocytes by the induction of IL-6, TNF-∝, and interferon, ***(Imani et al., 1993)***.AGE can react with and inactivate nitrous oxide (NO), a potent endothelium-derived vasodilator, antiaggregant, and antiproliferative factor ***(Bucula R, et al, 1991)*** and could play a role in the monocyte-mediated inflammatory disorders associated with uremia (***Witco et al, 1999)***.

Parathyroid hormone (PTH) (9 kDa):

PTH is generally recognized as a major uremic toxin. In excess it causes disturbances in the function of different organ