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Research Article

A NOVEL THERAPY TO REVERSE END STAGE KIDNEY RENAL DISEASE IN ITS EARLY STAGES 1 & 2 OR TO STABILIZE AND HALT ITS PROGRESSION IN MORE ADVANCES STAGES

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INTRODUCTION

Researcher

Rodolfo Gordillo M.D., MACP, and Nephro-immunologist from The Hospital Médica Sur, Mexico city. This research was planned all by myself both the study protocol and its execution, without participation of any other researcher. I declare I have not received any payment or grant by any private or governmental Institution nor any Medical Laboratory funds, therefore I have not any conflict of interest. I wrote and reviewed the document several times until its final version, and decided to send this paper to the Journal of the American Nephrology Association for their consideration to publish my research in their Journal. The reason to conduct this research is that the renal diseases represent a global problem with 850 million of renal patients most of them in their early stages but without knowing they have a renal disease and knowing that renal diseases started by an infectious or injury and consequently to this an inflammatory response is mounted by our innate immune system with subsequent damage and fibrosis. I hypothesized that by using a treatment to suppress that inflammatory response renal function would be preserved and improved.

Summary

Due to the increased incidence of chronic and progressive renal failure, the suffering of the patients and the high cost for their medical attention it was planned to develop a treatment to revert chronic renal failure or lentify its progression by controlling the non-infectious inflammatory process (sterile inflammation) caused by our own immunological innate system which reclute cells like macrophages, lymphocytes T and B that once activated release inflammatory cytokines 2nd Lymphokines like Interleukin-1(IL-1), Interlukin-6(IL-6) Macrophage attracting protein-1(MAP-1), Nuclear Factor-kb(NF-kβ), Necrosis Tumoral Factor-α (NTF-α), Transforming Growth Factor-β-(TGF-β) among others; the pleiotropic effects of some medications have a beneficial effect against inflammation by suppressing the synthesis of these substances. In 1984 in the JCI was published the Vitamin-D immunomodulators effects. Piolitazone was discovered to be an agonist of PPAR-γ receptors; it was also found to have effects over the suppression of these cytokines, and there is a recent publication stating that the nephroprotection provided by using Pioglitazone plus Losartan is better than Losartan alone [10].

Background

With the world wide increase of Obesity (35%), Systemic Hypertension(33%), Hyperuricemia(16%) and Proteinuria(6.1%) the incidence of Diabetes Mellitus type 2(DMT2) has increase dramatically(9%) as well as the incidence of Kidney Chronic Renal Failure(33%). Today there are in the world 850 million of patients with Kidney chronic renal failure most of them in the early stages (1&2) but even without knowing they have renal disease, this amount of patients is more than the double of patients in the world with type 2 Diabetes Mellitus which is around 420 million of patients (1) and is estimated that for the year 2025 will be a major increment in its prevalence. Today there are in the world 1,000,000 million patients under Dialysis treatment to whom 18,000 thousand patients are added yearly just in México to the number of patients on END STAGE KIDNEY DISEASE. In 2010 in USA 700,000 thousand patients where under Dialysis at a cost of 30 million dollars/year. In 2010 the global costs for the treatment of END STAGE KIDNEY DISEASE were 150 billion dollars and for 2025 is estimated it will increase to 300 billion dollars/year (2,3). The Wealthy and well Development

countries treat the mayor numbers of patients with END STAGE KIDNEY DISEASE with a Renal replacement function therapy (KIDNEY REPLACEMENT THERAPY (KRT)) but they do not treat all of them, and in the underdevelopment and poor countries the number of END STAGE KIDNEY DISEASE patients with a KIDNEY REPLACEMENT THERAPY (KRT) are much less in México we have from 98,000 to 136,500 thousand patients in END STAGE KIDNEY DISEASE plus from 16-18,000 thousand than added each year the number of patients under a KIDNEY REPLACEMENT THERAPY (KRT) is less than 7%. In Mexico usually the diagnosis of Diabetes Mellitus type 2 and Renal Failure (RF) are very delay as well as is the referral to the endocrinologist and to the nephrologist respectively, to the kidney doctor they arrive in stages 4 or 5 mostly to chose and program for a KIDNEY REPLACEMENT THERAPY (KRT) that for historical reasons most of the patients are directed to chronic ambulatory peritoneal dialysis 85% and only some 15% are placed in Hemodialysis (4), the performance of a Kidney Transplant either from a live related or a cadaveric donor is very low, because of idiosyncrasy, education, culture, the lack of modern legislation law for "Universal donor" and also for the lack of resources and capacity to perform more Transplantation even knowing that when done successfully is the only procedure that really rehabilitate the patient giving him the best life expectancy , no matter the patients' needs continuous surveillance, needs to take medicines for all his life and requires frequent laboratory studies. The novel treatment here described is directed against the factors that generate the progression of renal diseases and some of them are:

a) **Metabolic:** and need to be under control: like Hyperglycemia, Hyperuricemia, Hyperphosphatemia and the increase in Klotho Factor (5,6).

b) **Sterile Inflammation**: initiated by renal injury with the consequent activation of our innate immune system which induce recruitment of immune cells including macrophages, lymphocytes with the production of inflammatory Lymphokines and Cytokines that induce inflammation, damage and tissue fibrosis (7). Inflammation is initially a good response but it needs to be turned off, otherwise it turns into a deleterious chronic inflammatory disease with a bad outcome for the function of the specific organ. Currently this information has generated a great number of studies an assays focused on the inhibition of the production of theses Lymphokines and the obstruction of its binding to its specific receptors by the use of monoclonal antibodies (8).

In regard to this Novel Treatment for CKF there is not any precedent study and this is the first protocol directed to the inhibition of the production of low grade persistent inflammation due to the production of Lymphokines and cytokines that translate into renal damage with progression of the disease. It is not the ideal study because is not a rando-mized controlled trial (RCT). It is a Prospective, Longitudinal, Observational study with AT LEAST 10 years of follow up (Table 1) and in some cases upto 14 years.

The Health benefits to the patients with this therapy is that it improves their quality and expectative of life and as in its early stages (1,2) can revert the renal failure to normal renal function and in more advance stages (3,4) can stabilize renal function and slower its progression to ESKD, which are excellent benefits for the integral management of the patient increasing his compliance both with the diet plan and the medications, it also brings and economical benefit for the patient and for the National Health System that is why I believe that by proving that the treatment benefits are real it will bring a strong change in the way we treat renal patients.

We need to start with primary preventive medicine in persons with risk factors for renal disease inborn or acquired risks or both. This involves since infancy to avoid medication potentially nephrotoxic that are being use in excess like aminoglycoside antibiotics or the indiscriminate use of Non-X Steroidal Anti-inflammatory meds that the General Practitio- -ners and General Pediatricians abuse in their prescription and the list of potentially nephrotoxic medications is quite extensae and needs to be divulgated and known by all de Doctors in order to avoid their excessive use (Table 2).

The search for a treatment like the one I propose here has been search since nearly 20 years ago, in 2002 James C. Oates et al published that PPAR-r agonist could have a potential use for the treatment of Chronic Inflammatory Diseases like Type-2 Diabetes Mellitus, Psoriasis, Irritable Bowel syndrome, Rheumatoid Arthritis, Lupus Nephritis and even he emphasized its potential use for the treatment for prostatic, mamary and Bowel cancers (9). In 2006 several papers were published like the one from Stefand Sorand where he commented that the chronic use AT1 Angiotensin receptors blockers produced hypotrophy of the adipose tissue with a consequent increment of Adiponectin with its beneficial effects and the increase of PPAR-r receptors (10). Sarafidis published a bench to the patient bed research over the renal protection provided with thiazolidinedions (10) in the same year Giuseppe Remuzzi published X that the anti-proteinuric effect of Pioglitazone when added to is receptor was due at the molecular level to the transcriptional regulation of the expression of the gene encoding for the Nephrin protein esential in the Renal Filter (11), also AB Fogo published how the agonist for the PPAR-r receptors would protected the renal Podocytes (12). In 2007 Hui Min published that the renal protection was better by using Pioglitazone plus Losartan versus Losartan alone in patients with type-2 Diabetes Mellitus (13) and that thiazolidinedions increased the gene expression of Adiponectin and increase the levels of seric proteins. (Figure 1) (14) also PPAR have a role in the genetic expression of uncoupled proteins relevant to the muscle and páncreas (15) and therefore with the metabolism itself. Also has been published that thiazolidinedions decrease proteinuria, decrease the excessive deposit of glomerular matrix, of cellular proliferation, inflammation and fibrosis in patients with diabetic nephropathy (16), also it was discovered that they inhibit the migration of dendritic cells from the epithelium what decreases the inflammatory response (17), also decrease the Blood Pressure (18) decreasing the Cardiovascular risk. (Table 3).

Sabin Steffen published the immunomodulators effects of **Statins** and their possible beneficial effects for renal patients (18).

In 2014 Tetsu Akimoto published that the use of Febuxstat in patients with advance nephrophaty reduced the oxidative stress

Table 1: Caracteristicas De Pacientes Con Dmt2 Ingresados.

PT.No	INICIALES	SEXO	EDAD	CREATININA		UREA		ACIDO URICO		V.F.G.		MICROALBUMINURIA	
				mg/dl µmol/l		mg/dl mmol/l		mg/dl mmol/l		ml/min/1.73m2		µg/min	
				INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL
1	ARR	F	48	2.7/239	2.8/247	17.8/107	9.2/43.4	4.7/280	1.4/83	19	18	29.1	5.7
2	AMC	F	56	1.5/133	1.7/150	43.8/7.3	60/10	9.3/553	6/357	38	33	52	40
3	ALO	F	68	7.7/681	3.3/292	83/13.8	133/22.1	9.1/541	6.3/374	5.5	14.6	300	121
4	BEV	F	74	1.5/133	2.0/177	32.8/8.8	94.2/15.6	7.4/440	7.4/440	48	25	69.4	1.45
5	CEI	F	62	1.3/115	2.5/221	67.5/11.2	127/21.1	4.5/268	4.5/268	83	21	48	25.2
6	CMIV	M	68	1.5/133	1.3/115	40.8/6.8	49/83	7.9/470	1.7/101	40	42	46	0.4
7	CHCM	M	53	1.4/124	1.0/88.4	75.6/126	43/7.8	7.3/434	5.9/351	57	73.1	52	6.2
8	DPR	F	58	4.29/380	1.1/104.3	150/25	46.8/7.8	9.5/565	6.2/309	11	50	8.3	13.7
9	DEL	M	73	2.9/258	2.8/247	118/19.8	84/14	10.6/632	7/422	21	20	20.8	3.9
10	EFLM	F	64	1.42/126.4	1.6/140	64.2/10.7	69.8/11.6	6/357	5/297	39	36	31.2	20.8
11	FLC	F	64	1.3/115	0.9/79.5	46.4/7.7	24.1/4	4.2/250	3.2/196	42	63	14	0.4
12	GAL	M	62	1.6/142	1.4/128	62.4/10.4	63/10.5	10.8/648	1.3/76.7	45	51	3.1	1.1
13	GRJM	M	53	3.7/327	5.7/521	2.96/17	55.8/9.3	6.7/399	3.9/232	17.6	10.4	260	151
14	GSJA	M	59	3.2/283	5/442	22/137	21.8/131	6.1/363	2.8/167	20	12	32	58.5
15	HTC	F	71	1.4/124	1.1/97	78/13	45.7/7.6	2/119	3.2/190	38	49.4	0.27	0.27
16	JBMA	H	60	1.3/117	1.0/88.4	42.6/7	42/7	4/238	3.1/184	59	80.3	14	3.4
17	LEG	H	81	2/177	3.1/274	86/14.3	118/19.6	5.8/345	6/357	28	18	2804	261
18	LTJ	H	53	2.62/232	2/177	188/31.3	119/9.2	3/163	6.75/394	27	37	3.47	176
19	MSM	H	74	1.3/115	3.1/274	95/15.8	69.5/11.6	3.4/202	1.4/83	54	19	18	18.2
20	MAMaA	F	67	1.33/118	1.79/158	100.6/16.6	130.5/21.6	3.9/232	4.9/291	41	30	1.2	1
21	MUE	M	8	1.3/115	1.95/172	32.3/5.4	53/8.8	5.8/322	3.4/202	61	37	3	0.3
22	OMJL	M	60	1.8/158	1.2/106	47.3/7.9	49.8/8.3	5.5/128	4.7/279	50	65	5.76	0.27
23	PMH	M	47	1.4/124	13/115	50.7/8.4	40.8/6.8	2.4/143	2.7/160	58	63	7	1.1
24	PMJM	M	63	1.6/141	1.3/115	73.5/122	57.3/9.5	45/267.6	1.9/113	45	57	8	0.1
25	RGJ	M	47	1.3/115	1.22/108	52/8.6	35.4/5.9	4/238	3/184	64	65	0.62	0.14
26	RGMaL	F	66	1.3/115	0.9/79.5	50.4/8.4	35.9/5.9	6/357	4.6/275	43	65	24	0.97
27	SMF	M	83	1.99/168	2/177	64.2/10.7	366/30.5	4/238	5.9/355	32	33	20	11.4
28	SPS	M	71	1.4/128	15/132	60/9.9	31/5.2	7.4/440	3.8/230	48	45	14	12.5
29	SUD	F	89	1.3/115	1.3/115	74/12.3	71/11.7	4.9/291	1.4/83.2	35	34	4.8	8
30	SZMaL	F	66	1.3/115	1.28/114	79/13.2	78/13.1	9.1/547	4.8/291	43	42	4	4
31	TBA	M	49	2.1/186	1.0/88.4	49.87/8.3	44/7.4	6/357	5.2/315	36	73	0.8	0.9
32	TMM	M	51	2.1/189	0.98/86.6	32 4/5.4	20.4/3.4	8.6/511	6/366	35	83	7	5.4
33	TPM	F	62	1.3/115	1.1/103	101/16.8	76.8/12.8	1.8/464	4.8/285	44	47	3.2	0.6
34	VGJS	M	62	1.4/124	2.4/23	69/11.6	222/37	5.6/333	2.9/176	54	28	133	69
35	VGH	M	42	1.68/149	1.9/168	72.6/12.1	49/8.2	11.8/707	5.6/333	41	41	122	61.5
36	VSA	M	68	1.7/150	1.5/132	70/11.7	51.6/8.6	5.8/345	2.3/137	40	47	5	0.13
37	ZDG	F	79	1.3/115	1/88.4	55/9.1	91/15.2	7.8/464	3/178	39	70	69.4	0.55

Table 2: Pacientes Con Gota Y Síndrome Metabólico Ingresados Al Estudio

PT.N°	INICALES	SEXO	EDAD	CREATININA		UREA		ACIDOÚRICO		V.F.G.		MICROALBUMINURA	
				mg/dl µmol/l		mg/dl mmol/l		mg/dl mmol/l		ml/min/1.73 m2		µg/min	
				INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL
1	ACA	M	60	1.48/131	1.44/128	41.4/6.9	35/5.8	1.8/107	2.8/166	51	48	0.27	1.1
2	AMA	M	47	4.8/424	6.6/583	300/50	109/18	7.5/438	5.4/321	13	9	69.4	55
3	CRA	M	73	1.3/115	1.8/161	79/13.2	96/16	7.6/452	7.7/458	52	35	0.4	9
4	DFLE	F	73	1.3/115	1.8/161	72/12	107/17.8	6.7/398	3.3/196	41	27	0.44	0.2
5	DAMaJ	F	75	1.6/141	0.89/79.5	41/6.9	60/10	3.9/232	4.99/297	31	61	38	4.7
6	FPI	M	36	1.83/162	1.85/164	44/7.4	516/8.6	10.7/636	6.9/410	46	45	6	0.4
7	IFF	M	62	1.5/130	1.2/114	50.4/8.4	62/10.3	3.8/226	4.1/244	50	63	14	0.2
8	LCHL	M	66	1.3/115	1.6/141	42.6/7.1	75/12.6	5.8/345	3.7/220	57	43	4	0.4
9	IGI	M	41	8.7/755	1/88.4	72/12	27/4.5	14.2/845	7.3/440	5	92	25.7	0.14
10	LMN	M	55	1.32/117	1.19/106	4/19.9	29/4.9	17/101	6.8/404	61	67	0.27	0.13
11	MCF	M	78	1.4/125	1.1/105	40/6.8	52/8.7	7/416	3/179	47	58	0.14	3.4
12	OAE	M	67	2.2/194	3/295	69/11.6	102/17	8.2/488	6.8/404	30	20	20.8	61.8
13	OMCJ	M	75	1.4/124	0.75/66.8	45/7.5	57/9.5	5.6/333	7/426	49	67	0.4	0.5
14	RCHEA	F	70	2.1/187	1.5/139	33/5.5	60/10.1	9.9/589	5/297	23	33	1.6	1.3
15	RRA	F	88	1.4/123	21.9/168	77/12.8	77/12.8	4.6/274	5.6/333	34	23	0.15	1.38
16	RSP	M	84	2.3/203	1/88.4	107/17.8	426/7.1	7.4/440	3.3/196	25	69	0.4	9.7
17	SMA	F	56	1.5/133	2/177	64/10.7	73/12.1	6/357	1.4/83	38	26	4	2.5
18	SDAJ	M	27	2.9/256	2/177	63/10.6	60/10.1	5/297	1/59.5	28	44	3.5	6
19	TFC	M	43	1.8/158	0.7/62	94/15.7	27/45	45/267	53/315	34	105	4	0.1
20	DFLGE	M	53	2.29/203	2.3/210	98/163	95/15.9	4.89/291	4.8/286	31	30	7	1.25
21	GMJ	M	69	1.4/124	1.4/124	42.6/7.1	522,8.7	7.8/464	1.6/96	51	60	0.2	0.34
22	GSG	M	49	1.5/133	1/89.0	51.6/8.6	432/7.2	61/363	22/131	54	79	10.4	0.3
23	jCT	F	89	1.4/127	1.47/130	65/10.8	60/10.1	6.8/404	1.4/83	46	44	0.13	1.8
24	PSG	F	58	1.3/115	1/88.4	64/10.7	48,8	4.9/291	45/268	61	62	0.76	0.1
25	RMA	M	56	1.3/115	1.25/111	64/10.7	51/85	4.9/291	35/208	61	64	0.76	0.69
26	RVJM	M	47	1.6/141	1.48/131	38/6.3	56/93	63/380	2.7/260	51	55	2	0.2
27	SAG	F	56	1.5/130	1.2/109	72.7/12.1	61/10.2	4/238	3.4/203	39	46	0.5	0.34
28	VBPLF	M	56	1.4/124	1.24/110	31/5.2	25/4.1	5.9/351	3.7/220	56	63	1.4	0.07

(19). In 2016 the Group of the assay ESCAPE published that by maintaining a normal serum level of 25-hidroxi-Vitamin-D it was associa-ted with less proteinuria decreasing the renal failure and its progression in children with chronic renal failure (19). Finally in 2016 Dong Liu published a multicentric study showing that in patients with CKF the use of **Pentoxifylline** that inhibits inflammatory cytokines among them the TRANSFORMING GROWTH FACTOR β for Growth b that induce de-differentiation of epithelial cells to myofibroblasts and added to an increase of a secondary signal with increase of a-SMA increase the production of Collagen type III producing inflammation and fibrosis in the tubulo-interstitial space; the **Pentoxifylline** inhibit both effects, improving renal function (20,21). On the other hand the combination of IECA and ARB do not improve neither serum creatinine neither GFR but its use reduce proteinuria and attenuated the velocity of progression of renal disease (22,23). The results obtained in mentioned studies have not been encouraging and even there are discrepancies among them, many factors play a role as the design of the study, the selection of patients, the dosage of the medication, a reduce number of patients. For me after reading and analy-zing these studies I think that the confusion and lack of good results was BECAUSE that the medicines were employed in an isolated way and I think that to obtain enough potency to attenuate the inflammation all of them have to be used in conjunction.

In the Protocol that I designed before starting it I decided to use these SEVEN drugs: Pioglitazone (24), Pentoxifillina (25), Febuxstat (26), Atorvastatine (27). Poliunsaturated

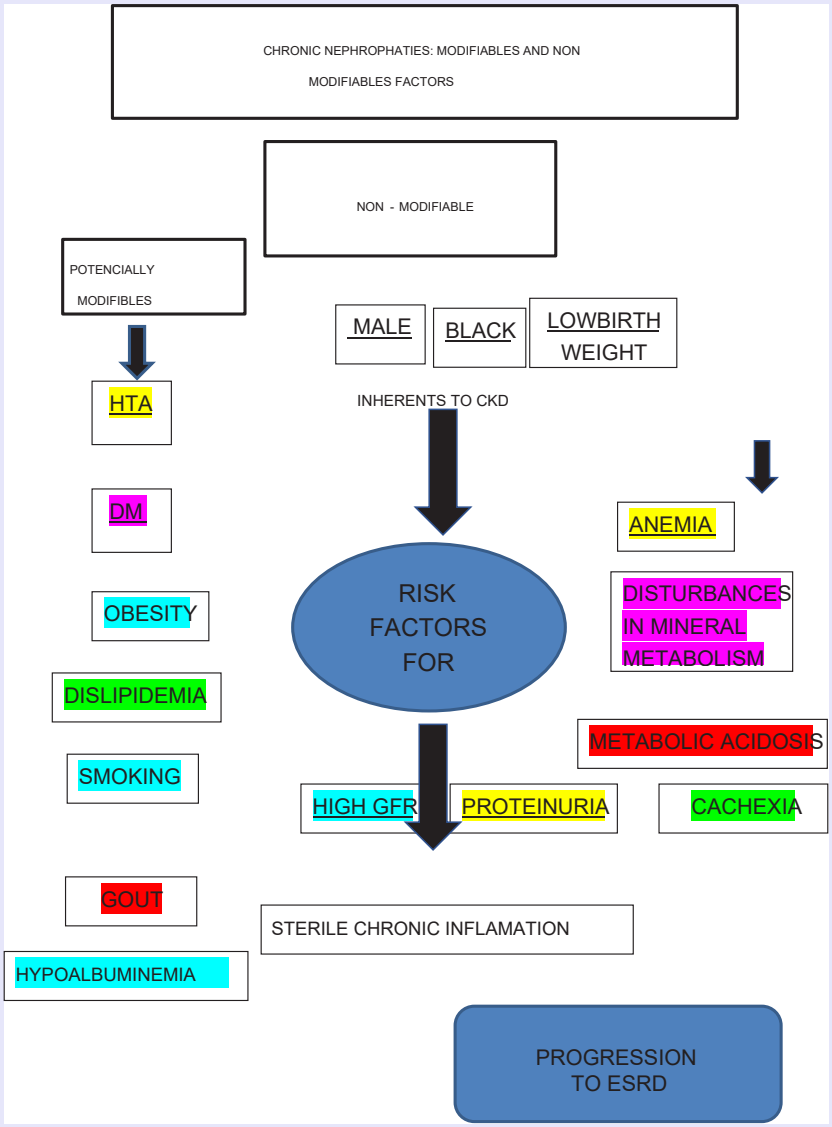

Figure 1 Chronic Nephrophaties: Modifiables And Non Modifiables Factors.

Table 3: Pacientes Con Hta, Enf. Autoinmunes Y Otras.

PT.N°	INICIALES	SEXO	EDAD	CREATININA		UREA		ÁODOÚRICO		V.F.G.		MICROALBUMINURIA	
				mg/dl µmol/l		mg/dl mmol/l		mg/dl mmol/l		ml/min/1.73m2		µg/min	
				INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL	INICIAL	FINAL
1	CGIA	M	67	1.4/124	1.4/124	43/7.1	43.2/7.2	3.3/196	2.5/148	52	37	1	0.13
2	CRS	M	64	1.7/150	1.6/141	35/5.87	52/8.7	11/654	3.6/220	42	44	1.7	1.94
3	DRJL	M	81	3/274	3/274	97/16.2	116/19.4	6.9/410	1.6/95	18	18	13.8	3.4
4	FAIL	M	68	1.4/125	1.5/132	47/7.8	45/7.5	3.2/190	4/240	50	47	15.3	11.8
5	GAF	M	74	2/177	2.6/230	71/11.8	87/14.5	4.4/262	3.5/208	17	23	14	2
6	GVS	M	49	2.2/194	4/353	57/9.6	95/15.9	7.2/428	3.4/202	25	12	52	1.1
7	LPV	M	85	1.7/152	1.3/117	81/13.5	53/8.9	6.4/380	3.3/196	35	48	14	0.15
8	MGMal	F	55	2.4/212	1.8/165	135/22.5	105/17.6	8.7/517	7.9/472	22	31	2.7	14.6
9	OSA	M	67	1.4/124	1.1/97.2	45/7.5	34/5.7	9/535	4.5/267	38	59	20.8	4
10	RRH	M	56	1.4/124	1/88.4	36/6.1	18.0/3.0	5.5/327	3/184	56	79	8	1
11	RVV	M	62	1.8/159	2.1/186	39.6/6.6	66/11.1	5.3/315	3.4/204	39	32	0.8	0.2

12	SVJR	M	76	1.3/115	1.4/124	46/7.7	45/7.5	6.1/363	4.1/244	53	49	0.5	1.3
13	VDM	M	65	1.3/115	1.7/150	27.6/4.6	59/9.8	5.5/327	3.9/235	53	40	0.24	0.2
14	FRB	F	81	5.38/476	1.7/150	98/16.3	60/10	3.5/208	4.7/279	7	28	8.4	27
15	RMA	M	67	1.4/124	1.45/129	41.4/6.9	39/6.5	4.9/291	3.6/214	52	51	0.27	0.13
16	RPM	M	69	1.23/109	1.33/117	50/8.3	21.5/3.5	4.7/279	4.7/279	69	63	0.5	0.4
17	GCA	F	32	1.4/124	4.9/433	68.4/11.4	130/22	9/535	8.9/529	50	11	1.3	41.5
18	ARMa	F	47	1.8/159	0.8/78.5	77/12.8	14/3.8	8/476	3/178	33	73	253	0.2
19	PSAP	F	10	1.4/124	1.2/106	58.5/9.7	41/6.8	6.4/381	3.6/214	65	97	0.83	1.3

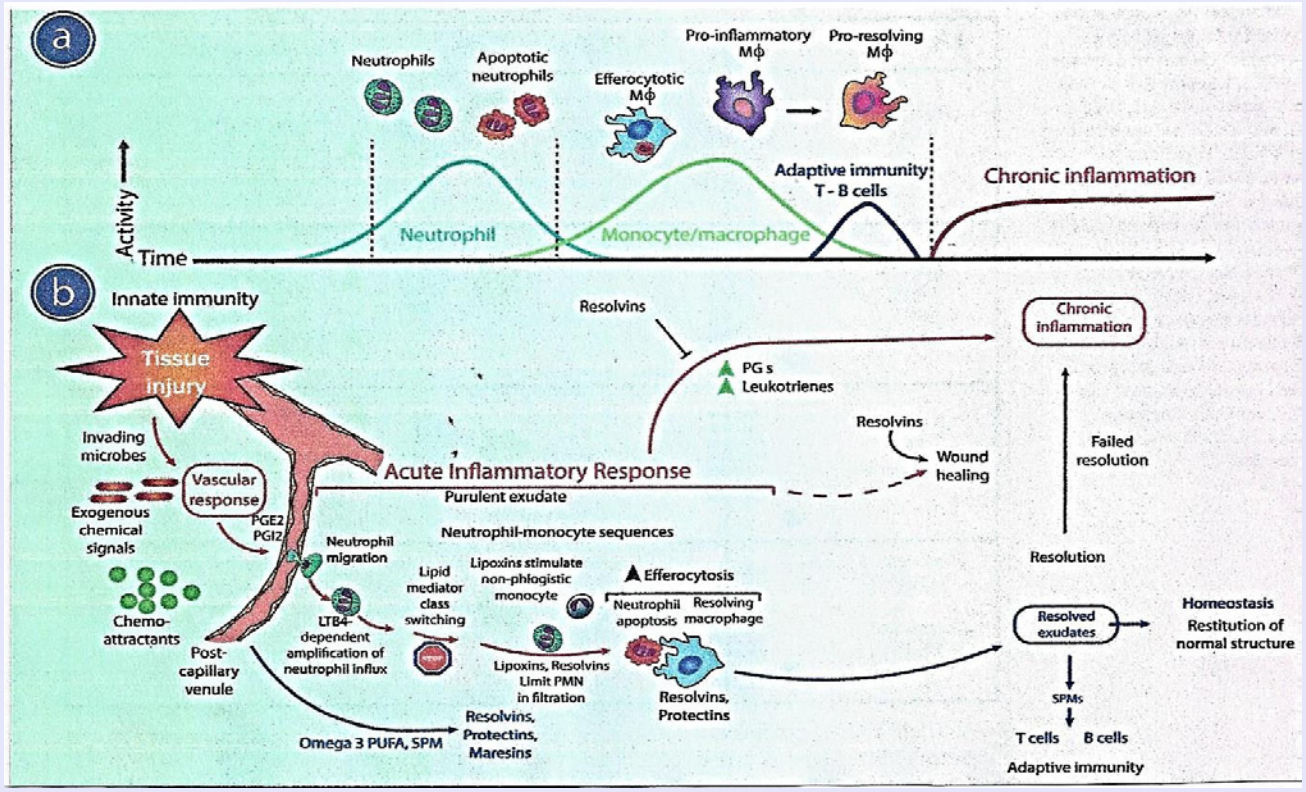

Figure 2 Mechanisms Of Sterile Inflamation With Resolution Or Without It : Chronicity.

Fatty Acids (PUFA) which derivates Protectins, Resolvins and Maresins and Vitamin-D (28) for its inmmunomodulatory effects, all of them act in the resolution of inflammation for its anti-inflammatory effects in the Kidney, and ARB (28) because with it we control hypertensión, decrease in the kidney the glomerular hyperfiltration, reducing the proteinuria (29) and by inhibiting the Renin-Angiotensin-Aldosterone system it inhibits the activation of the Transforming Growth Factor-β. I attribute the encouraging results of my protocol because of the use of this novel therapy 7 meds directed to attenuate the inate immune inflamation in association with the traditional treatment (30).

MATERIALS AND METHODS

Patients Selection

We included adolescents patients from 16 years old as an inferior limit and adults from all ages who suffered from CKF defined- with a serum creatinine of al least 115 mmol/l (1.3 mg/dl) with this criteria we included 88 Patients but 5 were excluded 3 because of not continuing the follow up and 2 because of stopping the therapy, therefore only 83 were left for analysis. We distributed them according to the primary disease etiologic factor of the Chronic Renal Failure. But before analyzing the results we will define the following terms. We considered a Positive Response to the therapy into 3 categories: **A) Excellent:** When the patient recovered the real function getting out to normal renal function and keeping there for at least 3 months. **B) Good:** When the patient improved his renal function, with a decrease of serum creatinine with at least a decrease of 0.3 mg/l and had a little improvement of GFR. **C) Positive:** When the patient stabilized his renal function although not improving his GFR but maintaining steady his renal function showing a slow down in the progression of his chronic renal failure. We considered a none Response when the patient continued his deterioration in his renal failure without a decrease in the velocity of loss of function.

Diabetes Mellitus: This was the greatest group with 37 pts.

23 males (62%), age range 51-85 years and 14 females (38%) age range from 56-98 years.

In this group the results were:

Excellent: 11 patients that came out from chronic renal failure to a normal renal function

Good: in 11 patients that improved his renal function with an increase in GFR but retain in CKF

Positive: in 7 patients that maintain its GFR within several years

None Response in: 5 that keep progressive deterioration in Kidney failure and 3 that got to End Point End Stage Renal Disease with the need of Renal replacement therapy**.** Therefore in this group 29 patients (78,4%) had a Positive response to the therapy and 8 did none responded to therapy.

Hyperuricemia: Was the 2nd largest group with 19 patients with 14 males and 5 females with an age range from 41 to 84 years old**.**

From the 19 patients the Results were:

Excellent response: 8 Patients (42.1%) improve their GFR and got a normal renal function.

Good response: in 5 patients (26.3%) that improved is GFR but stay in CKF.

None response in 8 patients 6 of them (31.5) deteriorate their renal function without reaching end point and 2 pts. reach end point and required Hemodialysis.In this Group there was a Positive response in 13 patients (68,4%)

Hypertension: Was composed by 13 patients, 12 males age range from 49 to 85 years and on female 55 years old.

The results from this group was an

Excellent response: 2 pts. (15.3%)

Good Response: 2 pts. (15.3%)

Positive response: 4 pts. (30.7%)

Non response 4 pts. (30.7%) , 1 patient reach end point because of dead secondary to heart infarctation In summary in this group we had a Positive response to the therapy in 8 patients (61.5%)

Metabolic Syndrome: Composed by 9 patients, 6 males age range from 47-69 years

In this group we had an excellent response:

Excellent: 4 pts. (44,4%) reach normal renal function,

Good: 2 (22.2%) patients improve renal function**,**

Positive: 3 pts, (33.3%) Nonresponders: 0.

In summary the 9 patients in this group had a Positive response (100%).

Other Pathology: 3 PATIENTS. One female 81 years old reach CRF because of recurrent Urinary Tract Infections, other patient a male 67 years old reach CRF because of excessive consumption of Non-Steroidal Anti-inflammatory Agents, and the last patient female 10 years old because of Uremic Hemolytic syndrome. The patients Results: The patient with UTI improved its renal function from a serum creatinine of 476 mmol/l (5.3 mg/dl) to 150 mmol/l (1.7 mg/dl) and an improvement of GFR from 7 ml/min/1.73m2 to 28 ml/min/1,73m2 SA.

The patient with Tubulo interstitial nephritis because of abuse of NSAI drugs, started the study with a serum cretinine of 124 mmol/l (1.4 mg/dl)and a GFR of 52 ml/min/1.73 m2 SA, and at the end of the study her serum creatinine was 129 mmol/l (1.45 mg/dl) and a GFR of 51 ml/min/1.73 m2 SA, so he maintained his renal function. The patient with CRF secondary to Hemolitic Uremic Syndrome started her disease at 6 monts of age, I started her management when she was 10 months of age and strated her therapy, the renal function was initially stable but started deteriorated slowly finally when she was 12 years old reached a serum creatinine of 124 mmol/l (1.4 mg/dl) and a GFR of 65 ml/min/ 1.73 m2 SA , at that time I started the new therapy and follow her for 11 years at the end her serum creatinine went down to 79.5mgol/2 (0.9mg/dl) and her GFR increased to 97 ml/min/1.73 m2 SA. In this small group the response to therapy was excellent in 1 patient (33.33%) and Good in 2 patients (66,66%) so we got a Positive response in 100%

Autoinmune Diseasses: Included only 2 patients one female 32 years old with Systemic Erythematosus Lupus with an initial serum creatinine of 124 mmol/l(1.4 mg/dl) and a GFR of 49.6 m l/min/1.73 m2 SA, wich started the therapy but had an inconsistent response she was also on Cell Cept 1.5 g/day and deflazacort 15 mg a day but 2 years later she reached her end point with a serum creatinine of 433 mmoil/l (4.9 mg/dl)and a GFR of 10.7 ml/min/1.73 m2 SA requiring a renal replacement therapy: Chronic Hemodialysis.

The 2nd patients was a female 47 years old with Rheumatoid Arthritis that started the study with a serum creatinine of 159 mmol/l (1.8 mg/dl) and a GFR of 33.4 ml/min/1.73 m2 of SA, she was also taking Cell Cept 1.5 g/day. After 10 years of follow up she ended with a serum creatinine of 78.5 mmol/l (0.8 mg/dl), and a final GFR of 73 ml/min/1.73 m2 In this small group of Autoinmune patients 0ne patient (50%) has an Excellent response coming back to a normal renal function and the other patients did not responded to the therapy an reached his end point (50%) So we got Excellent response in 50% of the patients.

RESULTS AND CONCLUSIONS

After the conclusion of this prospective longitudinal observational study with a follow up of 10-14 year carried in 83 patients we had the following results:

EXCELLENT RESPONSE with recovery of normal renal function in **28 pts (33.7%)**

GOOD RESPONSE with improving of their renal function in **20 patients (24%)**

POSITIVE RESPONSE with stabilizing of their renal function in **17 patients (20%)**

So That we have a POSITIVE RESPONSE IN: **65 PATIENTS (78.32%)** MORE THAN 2/3 OF THE TOTAL PATIENT NONRESPONDERS**: 18 patients (21.6%).**

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