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Preliminary study on efficacy and tolerance of a «coupage» of olive oil in patients with chronic kidney disease. Nutritional status assessment

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SUMMARY

The discrepancies among data reported by using olive oil (OO) in humans appear to be due to the great differences between the different OO used. Based on structure/function relationships we have chemically optimized an OO through the rational mixture («coupage») of several Spanish extra virgin olive oils (methodology «oHo»®). Patients with chronic kidney disease (CKD) develop a progressive picture of malnutrition and inflammation that lead them to an elevated risk of cardiovascular disease. In a pilot, randomised trial the nutritional efficacy and safety of «oHo» were evaluated in 32 patients (mean age 60,8 ± 13,2 years old; 16 women) with CKD (KDIGO stages 4-5) at predialysis. After a 7 days wash out for statins and ACE inhibitors 19 patients had «oHo» at doses of 60 mL/day (20 mL t.i.d) for 30 consecutive days, whilst 13 patients remain as a control group without «oHo». At the end of the study only patients having «oHo» showed significant increases of serum albumin ($p < 0.05$) and not significant increases of total proteins, weight, and BMI. Total cholesterol ($p < 0.05$) and HDL-cholesterol ($p < 0.01$) increased with «oHo». The number of cases with pathologic HOMA-IR in the control group increased from 1 to 2 patients whilst in the «oHo» group decreased from 2 to none. No significant changes of minerals, arterial pressure, hemoglobin, and other parameters related to CKD were seen. After a 30 days follow-up in the «oHo» group all parameters came back to basal ones, excepting for blood pressure that significantly decreased ($p < 0,05$). Tolerance was excellent and constipation significantly diminished ($p < 0,001$) in the «oHo» group. Of importance, none of these biological changes were seen in regular consumers of other conventional olive oils (control group). These intriguing results, seen by the first time, appear to partially satisfy the recent claims («reverse epidemiology») about the need of a more correct nutrition in CKD patients. However, these data need to be proved in more larger trials as well as in CKD patients under dialysis with harder inflammatory/malnutrition conditions.

Key words: ***Olive oil. «oHo». Chronic kidney disease. Malnutrition. Inflamation. HOMA.***

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ESTUDIO PRELIMINAR SOBRE EFICACIA Y TOLERANCIA DE UN «COUPAGE» DE ACEITE DE OLIVA EN PACIENTES CON ENFERMEDAD RENAL CRÓNICA. EVALUACIÓN DEL ESTADO DE NUTRICIÓN

RESUMEN

Las discrepancias en las acciones del aceite de oliva (AO) en humanos, parecen deberse a las diferencias existentes entre los distintos aceites utilizados en los estudios publicados, fundamentalmente en sujetos sanos. Basados en relaciones estructura/función, se ha optimizado químicamente un AO mediante la mezcla racional («coupage») de diversos aceites de oliva virgen extra españoles (metodología «oHo»®). Los pacientes con enfermedad renal crónica (ERC) desarrollan un cuadro progresivo de malnutrición e inflamación sobre el que asienta su elevado riesgo de enfermedad cardiovascular. En un estudio piloto, controlado y aleatorizado se ha evaluado la eficacia y seguridad de «oHo» en 32 pacientes (16 mujeres) con ERC (estadios 4-5) en prediálisis, (edad media 60,8 ± 13,2 años). Tras un período de lavado de 7 días para inhibidores de la ECA y estatinas, 19 pacientes tomaron «oHo» (60 ml/día, en 3 tomas) durante 30 días consecutivos y 13 permanecieron como grupo control. Al final del estudio, solamente los pacientes con «oHo» mostraron incrementos significativos en los niveles de albúmina sérica ($p < 0,05$), así como tendencia al aumento del peso y de las proteínas totales. Las cifras de colesterol total ($p < 0,05$) y HDL ($p < 0,01$) aumentaron en el grupo «oHo». El número de casos con HOMA patológico subió de 1 a 2 pacientes en el control, mientras que en el grupo «oHo» los 2 pacientes iniciales con HOMA patológico normalizaron sus índices. No se observaron cambios en los parámetros relacionados específicamente con la ERC: minerales, creatinina, anemia, etc. Tras un período de seguimiento de 30 días, todos los parámetros que cambiaron en el tratamiento regresaron a cifras basales, excepto la presión arterial media, que disminuyó ($p < 0,05$). La tolerancia fue excelente y el estreñimiento disminuyó significativamente (< 0,001) en el grupo «oHo». Dada la originalidad del estudio, estos resultados deberán ser comprobados con estudios más amplios.

Palabras clave: ***Aceite de oliva. «Coupage oHo». Enfermedad renal crónica. Malnutrición. Inflamación. HOMA.***

INTRODUCTION

Nutritional status is a key factor in the clinical course of patients with chronic renal disease (CRD).[1] Patients with CRD have high prevalence of malnourishment that presents æ from the beginning of the diseaseæ due to low levels of serum proteins together with weight loss, both conditions being related with increased morbidity and mortality rated.[1-3]

It is currently believed that malnourishment, partially due to uremia-induced anorexia, is not the cause of these changes and that muscle mass loss is due to endogenous proteolytic mechanisms.[4] In fact, it seems that hypoalbuminemia is not as much due to poor protein intake as to the presence of pathological conditions that promote these mechanisms, among which inflammation,[5] metabolic acidosis,[6] as well as other CRD-related pathologic conditions, such as insulin resistance (IR)[4] stand out. In any case, hypoalbuminemia is currently considered as: a) a cause and/or main consequence of malnourishment and inflammation in these patients; b) a known predicting factor of cardiovascular complications and of morbid-mortality increase in CRD patients, including those that have not started yet on dialysis.[1,7-9]

For all this, it is believed that correct dietary intake with several supplements, either orally or through intra-dialytic parenteral nutrition (IPN) with

essential amino acids, may be essential in the course of CRD.[3,10-12] More recently, the use of lipid emulsions based on soy and/or olive oils for IPN administration represents a new tool in nutritional management of CRD patients. Thus, it has been described that these emulsions to alleviate particular protein deficiencies including recovering of albumin serum levels.[13]

This rationale, together with the high costs associated with IPN,[10] led us to try to recover the nutritional status of our patients by means of olive oil (OO). It is today clear, however, that several of the beneficial actions ascribed to olive oil in humans are paradoxical and seem to depend on the type of OO used in each study as well as the pathological condition considered. In this way, although there is some consensus on the beneficial effects of virgin OO in patients with cardiovascular risk,[14] other contradictory effects on HDL-cholesterol[15-22] and on the IR phenomenon[20,23-29] in other pathologies have been described.

Strangely, a study on CRD patients reports on the lack of effect of OO on total cholesterol and HDL-cholesterol levels.[22]

Aside from these paradoxical actions of the different OO, it has not been considered either that some of them may contain substances interfering with their expected biological actions. Thus, pesticides and other synthetic chemical compounds behave as confounding factors for the endocrine system.[30] Since their presence in OO is often times higher than that contained in olives themselves,[31] it should be tried that olive oils used for patients are devoid of these substances. In the case we are dealing with, the reasonable doubt of their possible implication in the pathogenesis of several inflammatory diseases, including CRD itself, is emerging.[32-34]

For these reasons, together with other derived from several genetic and agrologic conditions inherent to the olive tree, it was decided to perform a first rational blend («coupage») of different extra organic/ecologic virgin OO in order to optimize their functional properties in humans.[35] This first organic «oHo» coupage is assessed in this nutritional study in patients with advanced CRD that will be completed with other ongoing immunological studies.

PATIENTS, MATERIAL AND METHODS

Patients: 32 patients (16 women), mean age 60.8 ± 12.8 years, diagnosed with CRD stages 4-5 of the KDIGO classification.[36] Other demographic and clinical characteristics are summarized in Table I. Patients were followed at the Pre-dialysis clinic of the Nephrology Department of the University Hospital of Jaen.

Inclusion criteria: Non-diabetic patients of both genders, older than 75 years, with advanced CRD that had not started on dialysis. They had not to present previous history of any disease that could interfere with the nutritional and inflammatory status of CRD, such as cancer, AIDS, hepatitis, tuberculosis, lupus, or rheumatoid arthritis, among others. During the 7 days prior to inclusion into the study (wash-out period), patients did not received any drugs that may affect the inflammatory reactivity such as steroids, ACE inhibitors (ACEI) or statins, although they may receive other conventional antihypertensive in case of necessary. All patients signed their informed consent. The study was approved by the Hospital's Ethic Committee.

Exclusion criteria: excluded patients were those with diabetes mellitus, congenital or acquired immunodeficiencies, with kidney or other grafts, obesity with BMI > 40 kg/m^2 and also those having received anti-inflammatory medications within 7 days prior to inclusion into the study.

«Coupage oHo» of organic olive oil: this is a rational blend (Methodology «oHo»®) from different extra virgin Spanish olive oils, which is based on a previous and comprehensive analysis of the qualitative and quantitative chemical composition of each oil used. Based on the known structural/functional relationships, the aim is to harmonize the presence of the components needed to do a particular biological function, in this case nutritional and anti-oxidant [the latter will be the subject of another publication]. All OO used came from organic (ecological) crops, endorsed by ecological accreditations (ACEA: Andalusian Committee of Ecological Agriculture), the final product being classified as extra virgin olive oil (Table II).[37] «oHo» was delivered bottled in dark glass labeled 500-mL bottles together with a dosing syringe and a recording log of the daily dose consumed by the patient. Each label contained the study number, the patient's code and initials as well as the date of delivery and recommendations for oil preservation and administration.

Analytical parameters: *a) Of efficacy*: the parameters analyzed were those directly related with the nutritional status (Table III), such as weight and body mass index (BMI), serum protein levels, lipid profile, glucose profile, as well as other indirect parameters

Table I. Demographical characteristics and CRD-related parameters

Characteristics	Study Groups: Control (w/o «oHo» oil)	Study Groups: «oHo»
Total patients (%)	13 (100%)	19 (100%)
Gender (M/F)	7/6	9/10
Age (years): X ± SD	61.4 ± 16.4	60.3 ± 10.1
• Women	59.5 ± 20.5	60.9 ± 10
	13 (100)	19 (100)
Usual OO consumers		
CRD parameters:		
• Creatinine clearance (mL/min)	18.9 ± 8.2	17.8 ± 7
• Urea clearance (mL/min)	8.5 ± 3.4	7.9 ± 2
• Plasma creatinine (mg/dL)	4.1 ± 2.1	4.8 ± 1.8
• Plasma urea (mg/dL)	133 ± 51	150 ± 42
	4 (30.7)	7 (36.8)
Num. and (%) of patientes in stage 5*		

OO: conventional olive oil; *According to the KDIGO classification[72]. No significant differences were found between groups.

Table II. Main components in «oHo»

Components	Values
FATTY ACIDS (%):	77.91
• **Mono unsaturated (MUFA):**	0.91
☐ Oleic	5.67
☐ Palmitolic	0.55
• **Poly unsaturated (PUFA):**	11.5
☐ Linoleic	2.85
☐ Linolenic	
• **Saturated (SFA):**	
☐ Palmitic	
☐ Stearic	
Total PHYTOSTEROLS (mg/kg)	1197
• Beta-sitosterol (%)	95.2
• Campesterol (%)	3
POLY PHENOLS (mg/kg)	10.93
• Hydroxytyrosol	0.01
• Oleuropein	0.63
• Vanillin	0.07
• Ferulic	
OTHER (mg/kg):	160.5
• Alfa- tocopherol (vitamin E)	1.5
• Beta-carotene (pro-vitamin A)	
FATS *trans* (*t*)	0.02 %
• Oleic *t* isomers	0.02 %
• Linoleic *t* + *t* Isomers	
WAXES (mg/kg)	38
PROTEINS	0
CARBOHYDRATES	0
PESTICIDES AND HERBICIDES	Not detected

«oHo» is an extra virgin olive oil, according to EEC Regulation 2568/91 and further modifications on vegetal fat consumption.[37]

(serum transaminase and homocysteine levels); ***b) of tolerability***: parameters related with the clinical situation of CRD (Table IV).

All the parameters were measured at the Clinical Laboratory Department of our hospital by using conventional diagnostic methods. Total proteins, albumin and homocysteine were assessed by nephelometry (Dade, Behring, Germany). Creatinine, urea, glucose, total triglycerides and HDL were deter-

Table III. Effects of «oHo» consumption for 30 days on nutritional parameters of CRD patients. Comparison with the Control Group that did not receive this olive oil

Nutritional Parameters	Assessment points / groups: Baseline (Day 0) Control n = 13	Baseline (Day 0) «oHo» n = 19	Final (Day +30) Control n = 13	Final (Day +30) «oHo» n = 19
NUTRITIONAL PROFILE				
Weight (kg)	66.6 ± 12.9	73.6 ± 10	66.5 ± 13	74 ± 10.8
Body mass index (kg/m^2)	27.9 ± 3.2	28.4 ± 4.6	27.8 ± 3.2	28.6 ± 4.8
Total proteins (g/dL)	6.95 ± 0.5	6.9 ± 1.3	6.9 ± 0.5	7.4 ± 0.5#
Albumin (g/dL)	4.1 ± 0.3	4.1 ± 0.8	4.0 ± 0.3	4.5 ± 0.4*
LIPID PROFILE				
Triglycerides (mg/dL)	112 ± 70.2	129 ± 62.7	115 ± 65.1	132 ± 51.4
Total cholesterol (mg/dL)	187 ± 44.2	192 ± 59.5	188 ± 50.7	214 ± 51.1*
LDL-cholesterol (mg/dL)	115 ± 28.9	114 ± 43.9	115 ± 38	124.3 ± 40
HDL-cholesterol (mg/dL)	49 ± 11	53 ± 16.3	50 ± 11.5	63 ± 20.9**
GLYCEMIC PROFILE				
Glucose (mg/dL)	89.2 ± 9.6	91 ± 14.7	88.5 ± 11.7	94.3 ± 8.6
Insulin (mU/mL)	9.4 ± 6.2	8.2 ± 3.4	10.5 ± 5.8	8 ± 2.7
HOMA index	2.1 ± 1.4	1.9 ± 0.97	2.2 ± 1.3	1.9 ± 0.69
Num. and (%) of cases with pathological HOMA index*	1 (7.7)	2 (10.5)	2 (15.4)	0 (0) [1 (5)]

N: number of evaluated cases; At baseline there were no significant differences between the study groups; # P = 0.056. * P < 0.05 and ** P < 0.01 vs. baseline and Control Group. The pathological HOMA index is defined here as ^{3}3,9 en women and ^{3}3,5 values in men. The figure between brackets represents the number of patients with pathological HOMA index during the follow-up period (day +60) in the «oHo» Group.

Table IV. Effects of «oHo» consumption for 30 days on directly CRD-dependent variables

Assessment points / Groups				
Parameters	**Baseline (Day 0)**		**Final (Day+ 30)**	
	Control n = 13	**«oHo» n = 19**	**Control n = 13**	**«oHo» n = 19**
Hemoglobin (g/dL)	12.3 ± 1.5	12.2 ± 0.8	12.3 ± 1.7	12.3 ± 0.8
Calcium (mg/dL)	9.3 ± 0.6	9.7 ± 1.4	9.3 ± 0.6	10.2 ± 0.6
Phosphorus (mg/dL)	4.2 ± 1.3	4.8 ± 1.3	4.2 ± 1.1	4.7 ± 1.2
Bicarbonate (mEq/L)	19.8 ± 3.7	21.4 ± 2.2	20.4 ± 3.8	20.9 ± 1.7
Urea (mg/dL)	133 ± 51	150 ± 42	138 ± 65	153 ± 39
Urea clearance (mL/minute)	8.5 ± 3.4	7.9 ± 2	8.06 ± 4.1	7.06 ± 2.5* [7.3 ± 2.7]
Plasma Cr. (mg/dL)	4.1 ± 2.1	4.8 ± 1.8	4.3 ± 2.2	5.1 ± 1.6
Cr. Clearance (mL/minute)	18.9 ± 8.2	17.8 ± 7	19.4 ± 10.3	14.7 ± 6* [16.7 ± 6.7]
intact PTH (pg/mL)	181 ± 134	216 ± 246	176 ± 85	256 ± 191
GOT (UI/L)	21 ± 10.3	16.5 ± 5.2	17.7 ± 6.9	19.4 ± 4.7* [16.3 ± 4.2]

Cr: Creatinine; N: number of cases evaluated. At baseline there were no significant differences between the study groups; * P < 0.05 vs. baseline. * P < 0.05 vs. baseline. The figures between brackets represent the values obtained during the follow-up period (day +60).

mined by enzymatic colorimetric methods adapted to an automatic Olympus 5400 analyzer. LDL-cholesterol was calculated by the Friedewald's formula. An ADVIA 120 counter (Bayer Diagnostic SL) was use for hemoglobin. Plasma insulin levels were determined by enzyme immunoanalysis (Axin, Abbott) and PTH by chemiluminescent method with a DXI 800 analyzer (Izasa SA). The HOMA-IR formula was used to calculate the insulin resistance index = [insulin (mU/mL) x glucose (mmol/L)]/22.5, where a high index reflects low sensibility to insulin.[38] A pathological HOMA was defined as ≥3,9 in women and ≥3,5 in men. Creatinine clearances and urea were calculated by the general clearance calculation (vol. min x urine parameter/blood parameter).

Other safety and tolerability clinical parameters

At the end of the period of oil consumption (day +30), patients were asked about the level of acceptance of «oHo» consumption, as well as the comfort or discomfort feeling experienced. Similarly, the number of cases having intestinal constipation at the beginning and at the end of the study was registered by means of a semi-quantitative question/answer scale. Constipation was considered to be present if: a) defecation was every two or more days; b) feces were of hard consistency; and c) there was discomfort when defecating.

Methods

During the month before entry into the study, patients were randomly assigned by order of arrival to consultation (odd or even order) to one of two study groups (Table I): Control Group, comprised by 13 patients (odd order of arrival) that did not received «oHo», and the «oHo» Group comprised by 19 patients (even order of arrival) that received «oHo». At day–1, each patient of the «oHo» Group received 4 bottles (2 L) of oil, a sufficient amount for the 30 study days. Each patient had to take 60 mL of «oHo»/day, distributed in three doses taken at breakfast, lunch, and dinner. The oil had to be always taken crude, directly taken or applied to natural foods from the diet, e.g., bread. During the study, patients were forbidden to take any other crude oil although they could still use their usual oils for cooking. We may point out that in our region (Jaen) it is routine practice in the general population to use olive oil, so that a especial emphasis was put on these recommendations (Table I). At baseline (day 0) and end of the study (day +30), all the clinical and laboratory parameters described were assessed.

Follow-up period

The group taking «oHo» was closely monitored throughout the 30 days following the end of olive oil consumption. At the end of this follow-up period (day +60 after the study beginning), all the panel of laboratory work-up above-mentioned was repeated in order to compare the control group and the «oHo» group.

Statistical analysis

For quantitative variables, the mean, median, standard deviation and maximal and minimal values were calculated. The sample was grouped according to the study group and the different variables measured at days 0, +30, and +60 were compared by non-parametric tests for related samples. Then, the incremental value between days 0 and +30 for the

different variables were calculated and the differences between the Control and «oHo» groups were compared by the Mann-Whitney test for independent samples. The McNemar' s test was used to compare the proportions in related samples. For those variables not following a normal distribution, such as PTH or alkaline phosphatase, a logarithmic transformation was used. The statistical analysis was done by means of the SPSS® statistical package for Windows, version 11.0.

RESULTS

Initial design and withdrawals from the study

This pilot study was designed aiming at studying the immunological changes produced by «oHo» consumption and, based on that, the sample size was calculated. Only 32 out of 40 (20 per group) expected patients strictly met the inclusion and exclusion criteria. During the first 15 study days, there were two withdrawals (one in the «oHo» Group and another one in the Control Group), because of having during this period continuous worsening of previous renal symptomatology that led to starting on dialysis. Three patients in the Control Group voluntarily withdrew from the study due to commuting problems, and three other withdrew at day–1 without giving any explanation. Due to the especial inclusion and exclusion characteristics, together with the need for blood samples in order to study the ongoing immunological changes (Second part of the study), these patients could not be replaced by other ones having similar characteristics to those initially recruited.

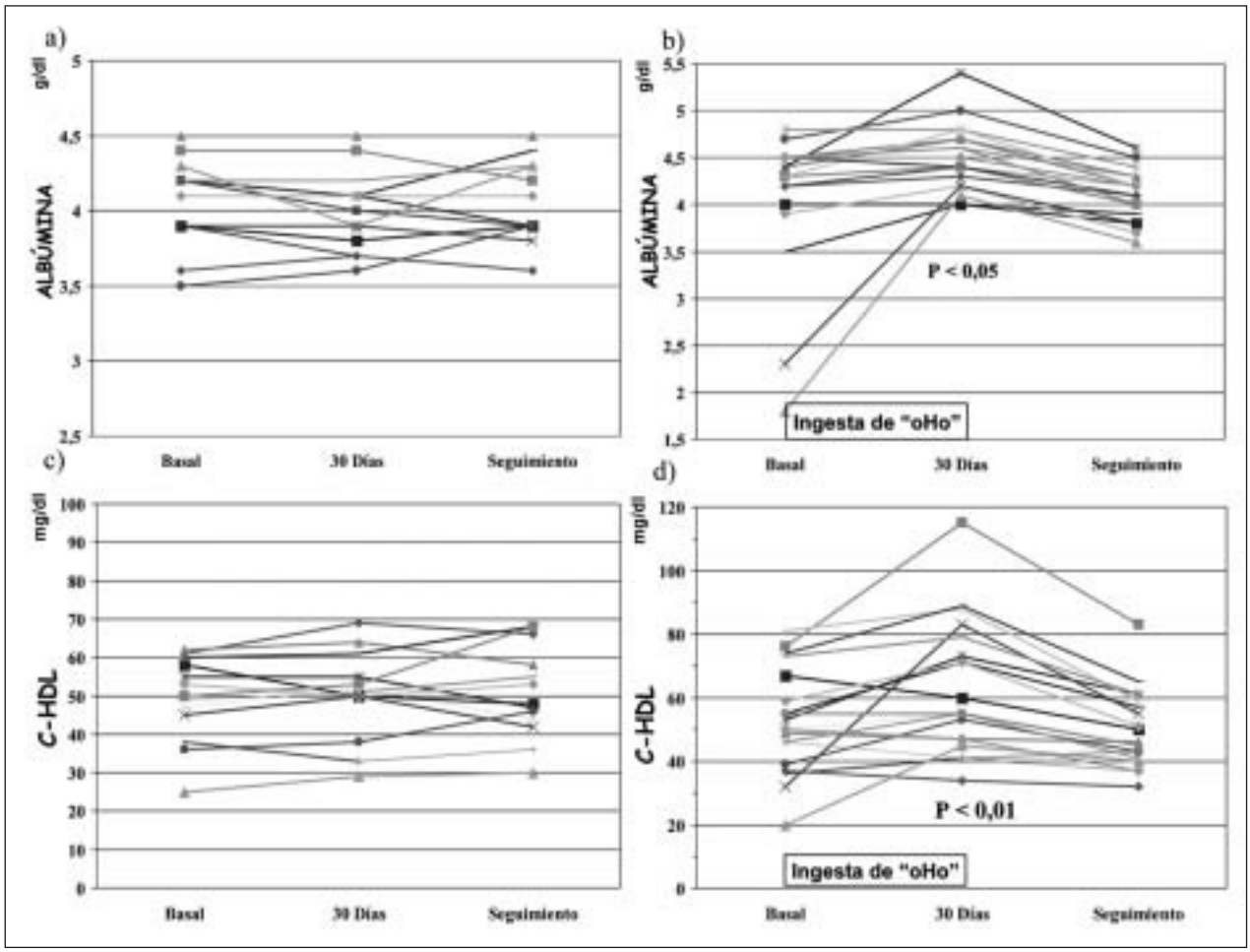


Fig. 1.—Progression of serum albumin (a and b) and HDL-cholesterol (c and d) levels observed during the study. Comparison between the Control Group (a and c) and that receiving «oHo» (b and d).

Characteristics of the patients finally included

Table I shows the demographical and CRD characteristics of the study population. At baseline, there were no significant differences in any of the parameters shown on the Table.

Nutritional status: profiles of proteins, lipids, and sugars. HOMA Index

During «oHo» consumption (Table III), no significant increases in weight and BMI were observed, as well as levels of plasma proteins ($p = 0.056$). These increases were significant for albumin ($p < 0.05$). In the Control Group, these parameters slightly decreased without reaching statistical significance (Table III). At day +60 (follow-up period in the «oHo» Group), all the nutritional parameters decreased (data not shown), returning to values similar to baseline ones. For instance, Figs. 1a and 1b show the progression of albumin during all the study period for both groups.

Triglycerides levels increased in a non-significant manner in both groups (Table III). Total cholesterol significantly increased ($p < 0.05$) in the «oHo» Group. LDL-cholesterol plasma levels did not change in any of the groups. HDL-cholesterol levels significantly increased ($p < 0.01$) only in the «oHo» group. During the follow-up period, triglycerides and LDL levels increased in a non-significant manner in both groups (data not shown), whereas HDL-cholesterol levels decreased in the «oHo» Group down to not showing significant differences with the baseline period (Figs. 1c and 1d).

There were no significant changes in sugar profile (Table III). In the Control Group one patient showed a pathological HOMA index at baseline, and this number increased to two patients throughout the study, whereas the two patients showing a pathological HOMA index at baseline in the «oHo» Group returned to normal (Table III). At the end of the follow-up period, one patient in the «oHo» Group presented once again a pathological HOMA index (Table III).

Minerals and other CRD-related parameters

In the «oHo» Group (Table IV), significant ($p < 0.05$) descents in urea and creatinine (without associated symptoms and with no need for changes in «oHo» administration), and not significant descents in phosphorus and bicarbonate levels were observed. Fig. 2a represents how the discontinuation of «oHo» consumption (follow-up, day +60) produced a return to baseline values.

Tolerability and safety parameters

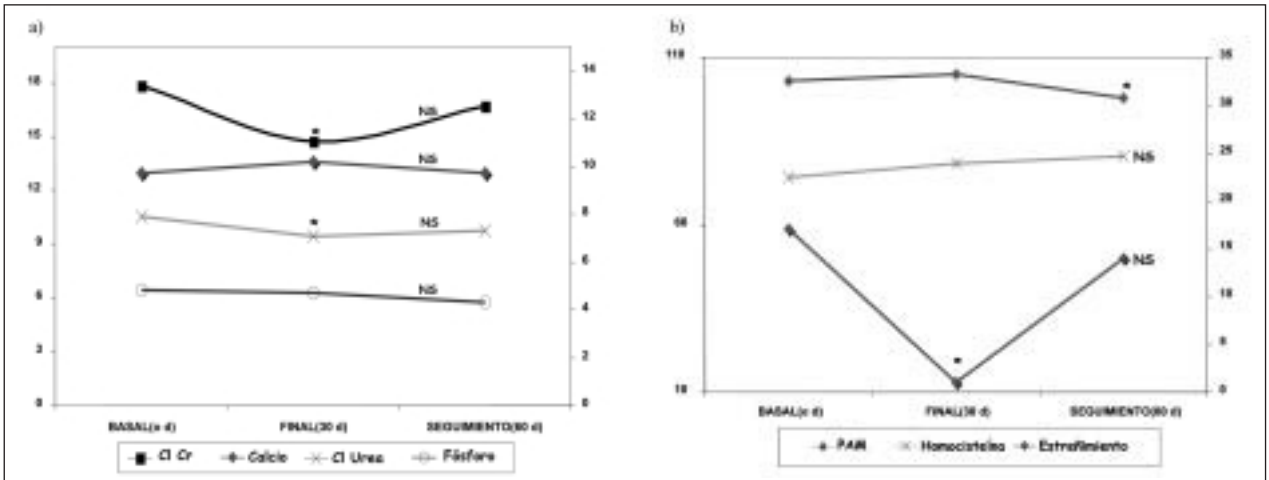
Between the baseline (day 0) and final (day +30) periods there were no changes in any group of the values for mean blood pressure, transaminase, GPT, and homocysteine (data not shown). The GOT values significantly increased ($p < 0.05$) in the «oHo» Group although it came back to during the follow-up period (Table IV). No changes regarding constipation were observed in the Control Group, whereas in the «oHo» Group this parameter significantly decreased during «oHo» consumption ($p < 0.001$) (Fig. 2b). Assessment at follow-up (day +60) in the «oHo» Group showed a return to baseline values of transaminase (GOT and GPT) and PTH levels, whereas homocysteine levels increased ($p < 0.05$) (Fig. 2b). The percentage of constipated patients returned to baseline values (Fig. 2b) and mean blood pressure (MBP) significantly decreased during the follow-up period ($p < 0.01$) as compared to baseline (Fig. 2b). Acceptance of «oHo» was excellent in all cases and no intake-related side effects were observed.

DISCUSSION

This is the first study aiming at verifying the nutritional effects of an olive oil in CRD patients. The results obtained indicate that nutritional supplement with and organic extra virgin «oHo» olive oil improves homeostasis within the protein, lipid, and glycidic compartments, while maintaining an adequate energy load and without side effects in patients with advanced CRD, stages 4-5. These effects fade upon discontinuing «oHo» consumption.

With regards to the protein compartment (Table III), the improvement in the nutritional status produced by «oHo» is represented by significant increased in weight (average of 400 g), BMI total plasma proteins levels; these increases might reach statistical significance by increasing the number of patients or the product administration time. In any case, 30 days of «oHo» administration were enough to significantly increase plasma albumin levels.

The increased in albumin observed are similar to those obtained with the use of other oral complex supplements [containing fat, proteins, anti-oxidant and anti-inflammatory agents][12] or olive and/or soy oil-containing emulsions used in IPN.[13,39-41] Whereas the methods cited base part of their composition in essential amino acids, it is evident that «oHo»



CrCl: creatinine clearance; UrCl: urea clearance. * P < 0.05 and ** P < 0.001 vs. baseline; NS: not significant as compared to baseline.

Fig. 2.—Progression of urea and creatinine clearances and calcium and phosphorus levels (2a) and values referred for mean blood pressure, homocysteine and constipation (2b) observed during the study period in the «oHo» group.

does not contain any protein material (Table II), clearly indicating that the mechanism of protein recovery observed in this study is not based on direct protein or protein-precursors consumption. Fortunately, an spite of the notable increase of protein nutritional status, the (not significant) increases in blood urea levels in the «oHo» Group were slightly lower to those observed in the Control Group (Table IV), indicating that consumption of the test product does not interfere with catabolic processes leading to increased urea production in CRD patients. Considering the close relationship between uremia and hypoalbuminemia,[6] these actions of the «oHo» could also contribute to nutritional status improvement. This improvement is achieved within 30 days, which is in contrast with the need for longer therapies, 3-12 months long, with IPN,[39-41] except for one study, and fades when the product is discontinued (Fig. 1b). This fact is the opposite to what has been observed in the Control Group (Fig. 1a), thus corroborating the truth of the described effects.

The impact of the nutritional effects of «oHo» on the inflammatory status of CRD patients are, until now, unknown, although there is a consensus on the close relationship between hypoalbuminemia and inflammation in these patients,[4,5,8,9,12] which already suggests the possible beneficial effect of «oHo».

About the lipidic compartment (Table III), improvement of the nutritional status was shown by significant increases in total cholesterol, mainly due to significant increases in HDL-cholesterol levels. These beneficial effects of «oHo» on the lipid profile are opposite to what has been observed with the use of olive oil emulsions for IPN, where total plasma fat content decreased by 50% and was accompanied by significant increases in LDL levels and significant decreases in HDL-cholesterol levels.[13] Other studies with soy oil emulsions in IPN[39] or with emulsions free from amino acids supplements[41] do not show either any effect on lipidic plasma composition in hemodialyzed patients. Similarly, although the effects of conventional OO on HDL-cholesterol levels in CRD patients are controversial,[15-21] one trial describes the lack of an effect of OO on total cholesterol and HDL-cholesterol levels in the CRD pathologic condition.[22]

The reality of these effects of «oHo» on HDL-cholesterol is represented in Fig. 1d that shows how the discontinuation of the product led to a decrease in HDL-cholesterol levels, by contrast to what happened in the Control Group (Fig. 1c). Consequently, and given the know cardiovascular protective effect ascribed to HDL in CRD patients,[42] the effects of «oHo» on this parameter should be regarded within its probable cardiovascular preventive dimension.

About sugars metabolism, an anecdotic decrease in the number of patients presented a pathological HOMA index at the study beginning, accompanied by a relapse during the follow-up period (Table III), suggests the positive effects of the product on IR. Given that the actions of conventional OO on HOMA-IR are controversial,[20,23-29] we will have to

wait until larger studies can clarify this situation.

In summary, taking into account that hypoalbuminemia, low HDL levels, and insulin resistance are potent predicting factors of the cardiovascular risk, morbidity and mortality in CRD patients,[1-13,42] the effects here described with «oHo» bring a new preventive and/or therapeutic alternative for these patients, always with appropriate caution.

The tolerability was excellent and no unwanted clinical side effects related with the product were observed. Consumption of «oHo» for 30 days did not change hemoglobin levels, the mineral profile, or urea and creatinine plasma levels (in spite of an increase in plasma proteins), although significant descents in urea and creatinine clearances were observed at the end of the administration period (Table IV). Regarding these latter functional changes, it seems clear that: 1) even from baseline, and just because of the random effect, the number of stage 5 CRD patients was higher in the «oHo» Group (Tables I and IV); 2) the decrease in clearances was not accompanied by other changes, such as decreased diuresis, increased acidosis, or increased hyperkalemia (data not shown); 3) these values returned to baseline values when «oHo» was discontinued (Fig. 2a); 4) nephrotoxic changes have never been described in relation with OO ingestion. It is evident that, given the state of advanced renal failure, these patients have no margins of physiological adaptation before the overload intake related with «oHo». Anyhow, the existence of these facts should be taken into account and verified in larger studies, especially in pre-dialysis patients.

Three other facts stand out in this preliminary study: 1) the dramatic decrease in the percentage of constipated patients during «oHo» consumption is a robust fact (Fig. 2b), which with no doubt has an impact on daily quality of life of CRD patients; 2) phosphorus values did not change or had a tendency to decrease (Fig. 2a), in spite of the nutritional status improvement; and 3) the behavior of mean blood pressure is also striking, which although it did not vary during «oHo» consumption, it significantly decreased during the follow-up period (Fig. 2b). Although we have not an explanation for this fact, it seems clear that conventional OO does not reduce blood pressure in CRD patients[22] under specific antihypertensive therapies.

Finally, we should point out the nutritional requirements of CRD patients that sometimes are very different from those of healthy individuals. Thus, the paradox claiming that, by contrast to what happens in healthy individuals («reverse epidemiology»), the poorer vital prognosis in CRD patients is directly related with low values of BMI, blood pressure and serum cholesterol, homocysteine, and creatinine levels, sets the need for interventional studies aiming at corroborating whether weight gain in CRD patients may increase their survival and improve their quality of life.[1] Besides, the ongoing immunological studies ought to clarify the unknown issues related with the nutritional status and the effects of «oHo».

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