

Olive oil in clinical nutrition

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RESUMEN

El aceite de oliva en nutrición clínica.

Los avances en el conocimiento del metabolismo lipídico están permitiendo establecer las bases científicas de los efectos saludables del aceite de oliva. En los países del área Mediterránea, la mortalidad cardiovascular es menor que en otros, aunque la concentración de colesterol en sangre es similar. Es muy probable que la capacidad cardio-protectora del aceite de oliva se relacione con otros factores de riesgo, algunos de los cuales son poco o completamente desconocidos. Las propiedades bioquímicas, biológicas y nutricionales del aceite de oliva son peculiares y permiten su aplicación en la nutrición clínica. Los beneficios del aceite de oliva se correlacionan con su acción sobre el metabolismo lipídico y el sistema cardiovascular. Un aumento moderado en la ingesta de grasa monoinsaturada (aceite de oliva), a expensas de los carbohidratos, es la recomendación en pacientes con diabetes e hipertrigliceridemia. En nutrición clínica, el aceite de oliva también tiene efectos beneficiosos en enfermedades relacionadas con respuestas inflamatorias y autoinmunes, como la artritis reumatoide. La composición química del aceite de oliva virgen extra contribuye a las necesidades diarias de ácidos grasos esenciales y de antioxidantes, especialmente en situaciones patológicas de deficiencia en vitamina E. Sin duda, el aceite de oliva (virgen extra) tiene máxima relevancia, por su contenido de ácido oleico (18:1n-9) y compuestos minoritarios, en la nutrición clínica.

PALABRAS-CLAVE: *Aceite de oliva; Ácidos grasos monoinsaturados; Nutrición enteral; Nutrición parenteral; Dieta Mediterránea.*

SUMMARY

Olive oil in clinical nutrition.

The different beneficial effects of olive oil have a rational and scientific basis due to advances in the knowledge of lipid metabolism. The evidence that for a similar plasma cholesterol concentration, the rate of cardiovascular deaths is lower in the

Mediterranean countries than in other ones, suggests that the beneficial effects of olive oil may not be only related to the known quantitative changes in plasma lipoproteins, but also to other, as yet unknown or little known, anti-atherogenic factors. The peculiarities of olive oil in terms of certain biochemical, biological and nutritional characteristics, open up a field of application in normal clinical practice. The benefits of olive oil in clinical nutrition correlate with its action on lipid metabolism and the cardiovascular system. Even a moderate increase in the ingestion of monounsaturated fats and a reduction in the ingestion of carbohydrates could be more advantageous in those patients with diabetes and hypertriglyceridemia and/or in those where loss of weight is not a priority. Different studies have also demonstrated the benefits of olive oil in different inflammatory and autoimmune diseases, such as rheumatoid arthritis. The chemical composition of extra virgin olive oil contributes to daily requirements of essential fatty acids and active antioxidant nutrients in vitamin E deficiency. This particular and well-balanced situation [oleic acid (18:1n-9) and minor components in an ideal ratio] undoubtedly has a significant relevance in human clinical nutrition.

KEY-WORDS: *Olive oil; Monounsaturated fatty acids; Enteral nutrition; Parenteral nutrition; Mediterranean diet.*

1. INTRODUCTION

Olive oil is not usual oil, as we can well see in this special edition of the journal *Grasas y Aceites*. The different beneficial effects of olive oil, known from time immemorial, today have a rational and scientific basis due to advances in the knowledge of lipid metabolism, as well as in other fields of biology, confirming epidemiological and nutritional data known for so many centuries.

The peculiarities of olive oil in terms of certain biochemical, biological and nutritional characteristics, open up a field of application in normal clinical practice. This includes the lipid component in enteral as well as in parenteral nutritional formulations. Anyway, it should keep in mind the importance of olive oil in oral nutrition under certain pathological conditions, such as those patients with disorders of carbohydrate and lipid metabolism, and other special conditions.

Strong evidence exists, derived from epidemiological, clinical and intervention studies, that the lipids in the diet, quantitatively and

qualitatively, are jointly responsible, along with the “new lifestyles”, for a series of diseases or pathological conditions coined as “*diseases of civilisation*”.

The establishment of a causal relationship between lipids in the diet and the concentration of cholesterol in the blood, high blood pressure and vascular disease, and other pathological conditions, drove the need to modify eating habits by reducing calories from saturated fats and increasing the ratio of monounsaturated to total fats.

2. OLIVE OIL AND ORAL NUTRITION

The tendency, in earlier times, to increase the ingestion of polyunsaturated fatty acids (PUFA), has been definitively shown to be less favourable, not only in the sense of inducing quantitative changes in the lipoprotein profile, but also in substantially decreasing the antioxidant potential of the food. This has led to the need to provide more antioxidant vitamins (e.g. vitamin E) to avoid the induced- or auto-oxidation of these PUFA and therefore increasing the aggression by reactive oxygen species (ROS) and lipid peroxidation.

Nutritionists, clinicians, epidemiologists and other professionals have recently directed their attention on the influence of olive oil in the diet for several reasons:

- Olive oil has unique physicochemical and sensorial characteristics.
- The historic consumption of olive oil in the Mediterranean area where, despite the high average ingestion of fats (approximately 40% of the total calories), the plasma cholesterol levels are relatively low.
- The evidence that for a similar plasma cholesterol concentration, the rate of cardiovascular deaths is lower in the Mediterranean countries than in other ones, which suggests that the beneficial effects of olive oil may not be only related to the known quantitative changes in plasma lipoproteins, but also to other, as yet unknown or little known, anti-atherogenic factors.
- Olive oil appears to be protective against certain tumours such as those found in breast, colon and prostate (Braga and La Vecchia, 1989; Newmark, 1999; Owen *et al.*, 2000a,b).
- The beneficial effects of a monounsaturated fat when it is substituted for saturated fatty acids (SFA) or carbohydrates in people with hypercholesterolemia or type 2 diabetes (Garg, 1998; ADA, 2002; Ros, 2003).

Moreover, the chemical composition of extra virgin olive oil contributes to daily requirements of essential fatty acids (*n*-6 and *n*-3 PUFA) and active antioxidant nutrients (tocopherols) in vitamin E deficiency. The phenolic and polyphenolic compounds present in extra virgin olive oil, with their high anti-oxidant power, act

as savers or protectors of tocopherols in different metabolic pathways, increasing in this way, directly or indirectly, the availability of high bioactive quantities of tocopherol to the cellular membranes. This particular and well-balanced situation [oleic acid (18:1*n*-9) and minor components in an ideal ratio] undoubtedly has a significant relevance in human clinical nutrition.

From the point of view of oral nutrition, different regional population studies, where distinct eating habits prevail, have clearly demonstrated the significant differences in the incidence and prevalence of death and morbidity in the pathologies related to cholesterol disturbances, such as cardiovascular and neoplastic diseases. One example of that is the classic “study of the seven countries” (Keys, 1980; Keys *et al.*, 1986). Compared to the diet of the countries in northern Europe, the Mediterranean Diet was associated to a low death rate for all causes and for ischaemic heart disease in the following fifteen years in the male cohort with ages between 40-50 years at the beginning of the study.

Traditionally, the benefits of olive oil in oral nutrition correlate with its action on lipid metabolism and the cardiovascular system. However, in the last few years, other beneficial effects of olive oil are of major interest in the field of gastroenterology. Olive oil may reduce the risk of cholelithiasis through multiple mechanisms, including its cholagogue effect by cholecystokinin stimulation (Baggio *et al.*, 1988; Bravo and Flora, 1998). Additionally, a diet rich in olive oil is associated with a high percentage of gastric peptic ulcer healing and acts as a resistance factor in gastric ulcerogenesis from non-steroidal anti-inflammatories. On the other hand, different studies have also demonstrated the benefits of olive oil in different inflammatory and autoimmune diseases, such as rheumatoid arthritis (Darlington and Ramsey, 1991). Cognitive protection against deterioration in the elderly is another clinical factor related to the intake of olive oil.

However, where possibly better evidence exists in oral nutrition, in relation to the benefits of monounsaturated fats and to olive oil in particular (apart from its benefits already mentioned regarding cholesterol metabolism and cardiovascular risk), it is in regard to its beneficial effects in patients with type 2 diabetes. In fact, the diet is a cornerstone in the treatment of these patients. The objective of dietetic management of patients with type 2 diabetes is not only to improve metabolic control of their hyperglycaemia but also, concomitantly and obligatory, to reduce the high cardiovascular risk (particularly for coronary disease) by optimising plasma cholesterol levels until they reach levels currently recommended for this population.

The development of type 2 diabetes is disposed to the high consumption of calories, especially of

fats, which used to be associated with development of obesity and overweight (Ohlsson *et al.*, 1985). However, studies carried out in the last decade have shown that the different fatty acids have different effects on carbohydrate metabolism. As the high consumption of PUFA induces a decrease in HDL cholesterol, along with the known effects on the oxidability of LDL (Hayne *et al.*, 1989; Swiburn *et al.*, 1991), it must not exceed the recommended 7% of the calories. By using different experimental models, monounsaturated fatty acids (MUFA) consumed instead of carbohydrates by patients with type 2 diabetes have the following effects (Garg *et al.*, 1988; Rasmussen *et al.*, 1993; Campbell *et al.*, 1994):

1. Improve the glucose tolerance and peripheral sensitivity to insulin.
2. Lower mean blood glucose and 24-hour urine glucose levels.
3. Lower the postprandial glucose, insulin and triglycerides.
4. Lower the requirements for exogenous insulin.
5. Lower the triglyceride levels and higher HDL cholesterol.
6. Decrease in numbers with high blood pressure.

However, diets rich in monounsaturated fats do not improve fasting glucose or HbA1C. When energy ingestion and weight is maintained constant, diets low in saturated fats and rich in carbohydrates or enriched with MUFA reduce the plasma HDL cholesterol values equivalently. The concern raised by this is that MUFA rich diets may increase energy consumption and weight in a voluntarily outside controlled environment. As earlier demonstrated in a meta-analysis (Garg, 1998), there is no evidence of weight increase in subjects with type 2 diabetes as long as energy intake is right.

Certainly, the latest recommendations of the American Diabetes Association include increasing carbohydrates or MUFA up to 60-70% of the total energy requirements to replace SFA (evidence level B) (ADA, 2002). Even a moderate increase in the ingestion of monounsaturated fats and a reduction in the ingestion of carbohydrates could be more advantageous in those patients with diabetes and hypertriglyceridemia and/or in those where loss of weight is not a priority.

3. OLIVE OIL IN CLINICAL NUTRITION: AN ALTERNATIVE LIPID

The peculiarities of olive oil that we have seen up to now, in terms of biochemical, biological and nutritional characteristics, open up a field of application in normal clinical practice as the lipid component in enteral and parenteral nutrition formulas.

Lipids are widely used in artificial nutrition, fundamentally for their high calorific value, isotonicity and their ability to "save" great quantities of carbohydrates, which can be harmful to critically ill patients. In fact, before the introduction of lipids into artificial nutrition and in emulsions, glucose was the only available source of non-protein calories that entailed on many occasions certain complications such as hepatic lipogenesis, a marked increase in carbon dioxide production and an increase in insulin requirements in diabetic patients.

The maximum tolerated carbohydrate load is 4 mg/kg/min in healthy subjects and 7 mg/kg/min in post-operative patients (Phillips and Odgers, 1986). Administering approximately 50% of non-protein calories in lipid form avoids the harmful effects of an excessive glucose load and results in a positive nitrogen balance (Nordenstrom *et al.*, 1983).

However, the introduction of lipids into artificial and parenteral nutrition signified a logical advance as a vehicle for energy and as a contributor of essential fatty acids, which the body cannot synthesize and has to obtain from the diet. The essential fatty acids [linoleic (18:2*n*-6) and -linolenic (18:3*n*-3) acids that belong to the *n*-6 and *n*-3 families, respectively] are the starting points for the elongation and desaturation mechanisms. There is the formation of more longer and unsaturated fatty acids, acting as structural elements in cell membranes and as precursors of highly bioactive eicosanoids (prostaglandins, leukotrienes and thromboxanes) by cyclo- and lipoxygenases coordinated pathways.

The initial developments in lipid emulsion for the formulation of parenteral diets used seed oils (soybean and sunflower oils) as the only fats, which predominantly contained triglycerides with long-chain unsaturated fatty acids from series *n*-6 and *n*-3 (Skeie *et al.*, 1983; Ekman *et al.*, 1987; Venus *et al.*, 1989; Kinsella and Lokesh, 1990). It was extremely high the concentration of PUFA and the ratio of linoleic acid to -linolenic acid, both in absolute and in relative terms, clearly exceeding the current daily recommendations. The total daily calories as linoleic acid should be 1-2%, with a contribution of -linolenic acid to reach a ratio of *n*-6/*n*-3 of around 4/1 to 10/1. As linoleic and -linolenic acids are involved into similar metabolic systems for the synthesis of their active metabolites, having -linolenic acid a higher affinity for those enzyme systems, any alteration in the concentration of *n*-3 fatty acids will have an effect on the metabolism of *n*-6 fatty acids.

Those formulations, based on only one class of seed oil, will be predisposed to produce non-balanced bioactive compounds at many cellular sites. They potentially induce different undesired pathologies, including thromboses, atheromatous

plaques, allergies, inflammations and even cellular proliferation phenomena. Highly unsaturated oils offer a "*fertilised field*" sensitive to ROS. By this way, free radicals continuously produced can damage all types of cellular macromolecules (proteins, lipids, carbohydrates and nucleic acids). If the exposure to these oxidative sources is intense and the material for its oxidation is highly reactive, the defence antioxidant mechanisms of the body can be insufficient for its neutralisation and lead to the well-known oxidative stress. This pathology is particularly serious in critically ill patients, the majority who are on parenteral nutrition, with no optimal antioxidant capability, and a high susceptibility to immunodepression and inflammatory processes (Halliwell and Gutteridge, 1985).

Therefore, in the last decade, it has made considerable efforts to develop new studies in clinical nutrition. The model mediates a decrease in the contribution of unsaturated fatty acids and modifies the pattern of lipids into the emulsions (BNF, 1993). Both conceptual changes have to improve distinct physiological responses. It appeared that olive oil has clear advantages by modulating the oleic acid content of emulsions and satisfying optimum ratios to the different fatty acid families (MUFA: oleic acid/*n*-6 PUFA: linoleic acid/*n*-3 PUFA: α -linolenic acid). The results of this new emulsion, in relation to the classic emulsion with soybean oil, show a similar supply of energy; beneficial effects on lipid metabolism (Aviram and Eias, 1993; Mangas-Cruz *et al.*, 2001); limited risk of lipid peroxidation both *in vitro* and *in vivo* due to the high content of MUFA and unsaponifiable rich in natural antioxidants (Scaccini *et al.*, 1992; Visioli *et al.*, 1994; Harris *et al.*, 1997; Visioli and Galli, 1998; Visioli *et al.*, 1998); and a more balanced production of long-chain PUFA. Olive oil is safety compare to other fats (Bach and Babayan, 1982; Liebermann *et al.*, 1990; Ythier-Moury *et al.*, 1990; Calder *et al.*, 1991; Garnier-Chevereau *et al.*, 1991; Brouwer *et al.*, 1993; Granato *et al.*, 2000) and supplies a fatty acid composition similar to those found in maternal milk (Tomarelli, 1988; Nestle NS, 1992), which once again reinforces the concept that olive oil is a dietary element of enormous biological value in clinical nutrition.

4. OLIVE OIL AND ENTERAL NUTRITION

Although a large amount of evidence exists on the benefits of olive oil as an integral part of the Mediterranean Diet, the data available on its effects as a component in enteral formulations is still scarce. Clinical trials carried out on different enteral formulations enriched with MUFA have been focused on specific clinical situations. Throughout this section, we will analyse the available data in the literature of two clinical situations of major interest,

the diabetic patient and the patient with active inflammatory intestinal disease.

4.1. Patients with diabetes mellitus

The dietary recommendations established for diabetic patients have varied throughout the time, due to greater knowledge of the disease, advances in nutrition and the treatment possibilities. Hyperglycaemia was early controlled at the expense of severe restricting carbohydrate intake. Later, diets very rich in carbohydrates were recommended, especially complex ones and with a large amount of fibre. Nowadays, the American Diabetes Association (ADA, 2003) has relaxed the restrictions on the amount of carbohydrates and MUFA, which contributes to personalize macronutrient intake depending on the type of diabetes, the nutritional status and the lipid profile (Franz *et al.*, 2002). Compared to diets enriched in carbohydrates, those rich in MUFA improve the glucose control and the lipid profile of patients with type 2 diabetes mellitus (Garg, 1998). Unfortunately, there is not the same level of confidence on the benefits of enteral formulations enriched in MUFA. It is reflected in ADA recommendations, where a standard formulation (50% carbohydrate) and formulations rich in fats and poor in carbohydrates can be found. We consider that enteral nutrition constitutes the first line nutritional support in practically all clinical situations. Therefore, it is of special interest to understand the influence of different enteral formulations on the metabolic control in diabetics (Sax and Souba, 1993). If high-MUFA enteral formula reproduces the favourable effects on glucose metabolism as shown for oral diets remains to be fully established and represents an active research line in clinical nutrition.

In 1989, Peters and Davidson reported a lower glycaemic response in 10 type 1 diabetic patients after stimulated tube feeding with a low-carbohydrate/high-MUFA/high-fibre enteral formula [16.7% of proteins, 50% of fats (35.7% as MUFA) and 33.3% of carbohydrates] compared to a high-carbohydrate/low-fat/low-fibre standard formula [16.7% of proteins, 30.1% of fats (0.4% as MUFA) and 53.2% of carbohydrates]. They concluded that the quantity of total carbohydrates in the formulation was the main determining factor in the glucose postprandial metabolism and that MUFA could be involved (Peters and Davidson, 1992). It was difficult to evaluate the role of MUFA in this experience, since the quantity of fats (MUFA) in the formulation varied as carbohydrates did.

The effect of MUFA-enriched enteral formula on glucose control in type 2 diabetic patients has been a focus of different studies (Sturner *et al.*, 1994; Sanz-Paris *et al.*, 1998; Thomas *et al.*, 1998). In some of them, a breakfast test has shown benefits by

reducing glucose and insulin plasma levels when MUFA replaced to complex carbohydrates. These findings were partially confirmed with a longer follow-up time (Craig *et al.*, 1998). Recently, we have collaborated in a Phase IV multicentre study for comparing the effect of two commercial formulations on the glucose metabolic control of 63 type 2 diabetic patients with indications of enteral nutritional support by nasogastric tube, due to neurological deficit or head/neck cancer surgery (Leon *et al.*, 2004). The first formulation, rich in MUFA and poor in carbohydrates, consisted of 16.7% of proteins, 50% of fats (3.8 g/100 mL of MUFA) and 33.3 % of carbohydrates; the second one was rich in complex carbohydrates and poor in fats [15% of proteins, 31% of fats (no MUFA) and 54% of carbohydrates]. The results obtained after a mean time treatment of 13 days showed that MUFA-enriched formulation had a neutral effect on plasma glucose control and lipid profile, and a better gastrointestinal tolerance, in comparison with the carbohydrate-enriched formulation.

4.2. Patients with inflammatory intestinal disease

When enteral nutrition is well tolerated, constitutes an efficient therapy in the treatment of Crohn's disease (CD). As shown previously, increased levels of *n*-6 PUFA enhance the formation of eicosanoids and cytokines with powerful pro-inflammatory action (James *et al.*, 2000), suggesting that diets rich in *n*-6 PUFA are not recommended under active CD. However, enteral formulation rich in oleic acid (olive oil) combined with steroids was found to be efficient against active CD but with a high variability in the rate of remission (Gonzalez-Huix *et al.*, 1993; Middleton *et al.*, 1995). Surprisingly, a recent study on 62 patients with active CD, the rate of remission in the group treated with enteral formulation rich in oleic acid (synthetic origin) was lower than that found with the formulation rich in linoleic acid (Gassull *et al.*, 2002). This effect was independent of the total amount of long-chain triglycerides (LCT) and differences could be partially attributed to the nature of the matrix fat from which oleic acid is supplied. In addition, we do not rule out the involvement of minor compounds from extra virgin olive oil on remission of active CD.

5. OLIVE OIL IN EMULSION FOR PARENTERAL NUTRITION

Parenteral nutrition contributes to the provision of amino acids and energy supply from glucose and lipids. Emulsions for parenteral nutrition may contain water, glycerol, egg yolk phospholipids, and soybean oil at concentrations of 20 to 30%, meaning the presence of LCT (Garcia de Lorenzo *et al.*, 2003). When used, the proportion of medium-chain

triglycerides (MCT) does not exceed 50% of total triglycerides (Garnacho-Montero *et al.*, 2002a). More recently, structured triglycerides with long- and medium-chain fatty acids in the glycerol backbone are also available.

Emulsions based on olive oil (EBOO: 80% olive oil and 20% soybean oil) have 20% SFA, 60% MUFA and 20% PUFA, and provide of α -tocopherol (36 mg/L vs. 9 mg/L from emulsions based on LCT). Animal studies show that EBOO improves hepatic regeneration after hemihepatectomy and induces not much lipid peroxidation and oxidative damage (Ok *et al.*, 2003). In traumatised patients, subjected to parenteral nutrition with EBOO there is an increase in the plasma levels of vitamin E as compared with soybean oil-containing emulsion (Bernard *et al.*, 2000; Reimer *et al.*, 2000). In a randomised double-blind study on burns patients, Garcia de Lorenzo *et al.* (2000) observed that the EBOO-group maintained adequate plasma levels of essential fatty acids compared to the group treated with MCT/LCT. Similar results have been described for children after EBOO for 2 months (Goulet *et al.*, 1999). Compared to soybean oil, they better tolerated EBOO and exhibited a lower peroxidation index.

In several clinical studies, the use of LCT for parenteral nutrition has been associated with growth of bacteria in catheter of surgical patients (Snydman *et al.*, 1982), bacteraemia in critical ill neonates (Freeman *et al.*, 1990), and pneumonias and infections related to the catheter in traumatised patients (Battistella *et al.*, 1997). The role of PGE₂ in these processes is a matter of discussion. PGE₂ has different immunomodulatory effects depending on its concentration: higher than 10⁻⁹ M is capable of activating T suppressor cells and suppressing blastogenesis of T and B cells, production of certain cytokines and immunoglobulins, mitogen response and phagocyte function; whereas lower than 10⁻⁹ M promotes lymphocyte differentiation and formation of antibodies. EBOO may achieve a decrease in PGE₂, but it remains to be established if the effect continues in critical situations, such as advanced sepsis, severe burns or multiple traumas.

Another clinical aspect of EBOO is its ability to maintain the integrity of the intestinal barrier, conferring a new dimension to these emulsions that goes beyond a simple qualitative nutritional substitution. Our group has verified that EBOO induces less bacterial translocation compared to classic emulsions with LCT and LCT/MCT (Garnacho-Montero *et al.*, 1999). Additionally, we have shown by using an animal model that this effect operates with a minor depression in phagocyte capacity of the mononuclear system after a bacteraemia with Gram-negative bacilli (Garnacho-Montero *et al.*, 2002b), and with an atrophy of the intestinal epithelial cells, especially in the jejunum (Ortiz-Leyba *et al.*, 2001).

REFERENCES

- ADA, American Diabetes Association. (2002). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*, **25**, 148-198.
- ADA, American Diabetes Association (2003). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*, **26**, S51-S61.
- Aviram, M., Elias, K. (1993). Dietary olive oil reduces low-density lipoprotein uptake by macrophages and decreases the susceptibility of the lipoprotein to undergo lipid peroxidation. *Ann. Nutr. Metab.*, **37**, 75-84.
- Bach, A., Babayan, V.K. (1982). Medium chain triglycerides: An update. *Am. J. Clin. Nutr.*, **36**, 950-962.
- Baggio, G., Pagnan, A., Muraca, M., Martin, S., Oportuno, A., Bonanome, A., *et al.* (1988). Olive oil enriched diet: effect on serum lipoprotein levels and biliary cholesterol saturation. *Am. J. Clin. Nutr.*, **47**, 960-964.
- Battistella, F.D., Widergren, J.T., Anderson, J.T., Siepler, J.K., Weber, J.C., MacColl, K.A. (1997). Prospective, randomised trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J. Trauma*, **43**, 52-60.
- Bernard, N., Morau, D., Bosc, A., *et al.* (2000). Parenteral lipid emulsions: effects on vitamin E in intensive care unit patients (short infusion). *Clin. Nutr.*, **19**, 21.
- Braga, C., La Vecchia, C. (1989). Olive oil, other seasoning fats, and the risk of colorectal carcinoma. *Cancer*, **82**, 448-453.
- Bravo, E., Flora, L. (1998). The influence of dietary saturated and unsaturated fat on hepatic cholesterol metabolism and the biliary excretion of chylomicron cholesterol in the rat. *Biochim. Biophys. Acta*, **1390**, 134-148.
- BNF, British Nutrition Foundation (1993). Unsaturated fatty acids: nutritional and physiological significance. The report of the British Foundation's task force. Chapter 22. Recommendation for intakes of unsaturated fatty acids. Ed. Chapman and Hall. London.
- Brouwer, C.B., de Bruin, T.W., Jansen, H., Erkelens, D.W. (1993). Different clearance of intravenously administered olive oil and soybean oil emulsion: role of hepatic lipase. *Am. J. Clin. Nutr.*, **57**, 533-539.
- Calder, P.C., Bond, J.A., Bevan, S.J., Hunt, S.V., Newsholme, E.A. (1991). Effect of fatty acids on the proliferation of concavalin A-stimulated rat lymphocytes. *Int. J. Biochem.*, **23**, 579-588.
- Campbell, L.V., Marmot, P.E., Dyer, J.A., Borkman, M., Storlien, L.H. (1994). The high-monounsaturated fat diet as a practical alternative for non-insulin-dependent diabetes mellitus. *Diabetes Care*, **17**, 177-182.
- Craig, L.D., Nicholson, S., Silverstone, F.A., Kennedy, R.D. (1998). Use of a reduced-carbohydrate, modified-fat enteral formula for improving metabolic control and clinical outcomes in long-term care residents with type 2 diabetes: results of a pilot trial. *Nutrition*, **14**, 529-534.
- Darlington, L., Ramsey, N. (1991). Is diet important in rheumatoid arthritis?. *Br. J. Rheumatol.*, **26**, 315-316.
- Ekman, L., Wretling, A., Moldauer, L. (1987). New developments in lipid emulsions for parenteral nutrition. *Infusionsther. Klin. Ernahr.*, **14**, 4-8.
- Franz, M.J., Bantle, J.P., Beebe, C.A., Brunzell, J.D., Chiasson, J.L., Garg, A., *et al.* (2002). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*, **25**, 148-198.
- Freeman, J., Goldman, D.A., Smith, N.E., Sidebottom, D.G., Epsten, M.F., Platt, R. (1990). Association of intravenous lipid emulsion and coagulase-negative Staphylococcal bacteraemia in neonatal intensive care units. *N. Engl. J. Med.*, **323**, 301-308.
- Garcia de Lorenzo, A., Denia, R., Martinez Ratero, S., *et al.* (2000). Randomized, double-blind study in severely burned patients under short term parenteral nutrition (TPN) with a new olive oil based lipid emulsion vs. TCM/TCL lipid emulsion (LE). *Clin. Nutr.*, **19**, 43.
- Garcia de Lorenzo, A., Lopez-Martinez, J., Planas, M., Chacon, P., Montejo, J.C., Bonet, A., Ortiz-Leyba, C., Sanchez-Segura, J.M., Ordonez, J., Acosta, J., Grau, T., Jiménez, F.J. (2003). Safety and metabolic tolerance of a concentrated long-chain triglyceride lipid emulsion in critically ill septic and trauma patients. *JPEN*, **27**, 208-215.
- Garg, A. (1998). High-monounsaturated-fat diets for patients with diabetes mellitus: a metaanalysis. *Am. J. Clin. Nutr.*, **67**, 577S-582S.
- Garg, A., Bonanone, A., Grundy, S.M., Zhang, Z.J., Unger, R.H. (1988). Comparison of high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. *N. Engl. J. Med.*, **319**, 829-834.
- Garnacho-Montero, J., Garnacho-Montero, M.C., Ortiz-Leyba, C., Garcia Garmendia, J.L., Jimenez-Jimenez, F.J., Perez Paredes, C., Moyano del Estad, M.R., Momtarrubio J. (1999). Bacterial translocation can be ameliorated using different intravenous lipid emulsions. *JPEN*, **23**, S15.
- Garnacho-Montero, J., Ortiz-Leyba, C., Jimenez-Jimenez, F.J., Garcia Garmendia, J.L., Jimenez-Jimenez, L.M., Barrero-Almodovar, A.E., Garnacho-Montero, M.C. (2002a). Clinical and metabolic effects of two lipid emulsions on parenteral nutrition of septic patients. *Nutrition*, **18**, 134-138.
- Garnacho-Montero, J., Ortiz-Leyba, C., Garnacho-Montero, M.C., Garcia Garmendia, J.L., Perez-Paredes, C., Moyano del Estad, M.R., Barrero-Almodovar, A.E., Jimenez-Jimenez, F.J. (2002b). Effects of three intravenous lipid emulsions on survival and the mononuclear phagocyte function of septic rats. *Nutrition*, **18**, 751-754.
- Garnier-Chevereau, F., Ythier-Moury, P., Dutot, G., Melin, C. (1991). Hepatobiliary modification associated with TPN in rats; influence of different components of lipid emulsions. *Clin. Nutr.*, **10**, 47.
- Gassull, M.A., Fernandez-Bañares, F., Cabre, E., Papo, M., Gaffer, M.H., Sanchez-Lombraña, J.L., *et al.* (2002). Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohns disease: results of a double blind randomised multicentre European trial. *Gut*, **51**, 164-168.
- Gonzalez-Huix, F., de Leon, R., Fernandez-Bañares, F., *et al.* (1993). Polymeric enteral diets as primary treatment of active Crohns disease: a prospective steroid controlled trial. *Gut*, **34**, 778-782.
- Goulet, O., de Potter, S., Antevi, H., *et al.* (1999). Long-term efficacy and safety of a new olive oil based intravenous fat emulsion in paediatric patients: a double-blind randomized study. *Am. J. Clin. Nutr.*, **70**, 338-345.
- Granato, D., Blum, S., Rossie, C., Le Boucher, J., Malnoe, A., Dutot, G. (2000). Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro. *JPEN*, **24**, 113-118.
- Halliwell, B., Gutteridge, J.M.C. (1985). Free Radicals in Biology and Medicine. Ed. Oxford-Clarendon.

- Harris, W.S., Rambj, G.S., Windsor, S.L., Diederich, D. (1997). N-3 fatty acids and urinary excretion of nitric oxide metabolites in humans. *Am. J. Clin. Nutr.*, **65**, 459-464.
- Hayne, R.J., Mulder, C., Popp-Snijders, C., Van der Meer, J., Van der Veen, E.A. (1989). Linoleic-acid-enriched diet: long-term effects on serum lipoprotein and apolipoprotein concentrations and insulin sensitivity in non-insulin dependent diabetic patients. *Am. J. Clin. Nutr.*, **49**, 448-456.
- James, M.J., Gibson, R.A., Cleland, L.G. (2000). Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am. J. Clin. Nutr.*, **71**, 343S-348S.
- Keys, A. (1980). Seven Countries Study: A multivariate analysis of death and coronary heart disease. A Commonwealth Fund Book. Cambridge: Harvard University Press.
- Keys, A., Menotti, A., Karvonen, M.J., Aravanis, C., Blackburn, H., Buzina, R., *et al.* (1986). The diet and 15-year death rate in the Seven Countries Study. *Am. J. Epidemiol.*, **124**, 903-915.
- Kinsella, J.E., Lokesh, B. (1990). Dietary lipids, eicosanoids and the immune system. *Crit. Care Med.*, **18**, S94-S113.
- Leon, M., Garcia-Luna, P.P., Planas, M., Sanz-Paris, A., Gomez-Candela, C., Casimiro, C., the Abbott SPAI-97-004 Study Cooperative Group. (2004). Glycaemic and lipid control in hospitalized Type 2 diabetic patients: Evaluation of two formulas for enteral nutrition. In press.
- Liebermann, M.D., Shou, J., Torres, A.S., Weintraub, F., Goldfine, J., Sigal, R., Daly, J.M. (1990). Effect of nutrient substrates on immune function. *Nutrition*, **6**, 88-91.
- Mangas-Cruz, M.A., Fernandez-Moyano, A., Albi, T., Guinda, A., Relimpio, F., Lanzon, A., Pereira, J.L., Serrera, J.L., Montilla, C., Astorga, R., Garcia-Luna, P.P. (2001). Effects of minor constituents (non-glyceride compounds) of virgin olive oil on plasma lipid concentrations in male Wistar rats. *Clin. Nutr.*, **20**, 211-215.
- Middleton, S.J., Rucker, J.T., Kirby, G.A., *et al.* (1995). Long-chain triglycerides reduce the efficacy of enteral feeds in patients with active Crohns disease. *Clin. Nutr.*, **14**, 229-236.
- Nestle nutrition services (1992). Polyunsaturated fatty acids in human nutrition. Ed. Bracco, U., Deckelbaum, R.J. Reaven press, New-York, USA.
- Newmark, H.L. (1999). Squalene, olive oil, and cancer risk. Review and hypothesis. *Ann. N. Y. Acad. Sci.*, **889**, 193-203.
- Nordenstrom, J., Askanazi, J., Elwyn, D.H., Martin, P., Carpentier, Y.A., Robin, A.P., Kinney, J.M. (1983). Nitrogen balance during TPN: glucose vs fat. *Ann. Surg.*, **197**, 27-33.
- Ohlsson, L.O., Larsson, B., Svärdsudd, K., Welin, L., Erikson, H., Wilhelmsen, L., *et al.* (1985). The influence of body fat distribution on the incidence of diabetes mellitus: 13.5-year follow-up of the participants in the study of men born 1913. *Diabetes*, **34**, 1055-1058.
- Ok, E., Yilmaz, Z., Karakucuk, I., Akgun, H., Sahin, H. (2003). Use of olive oil based emulsions as an alternative to soybean oil based emulsion in total parenteral nutrition and their effects on liver regeneration following hepatic resection in rats. *Ann. Nutr. Metab.*, **47**, 221-227.
- Ortiz-Leyba, C., Jiménez-Jimenez, F.J., Garnacho-Montero, J., Garcia Garmendia, J.L. (2001). Nuevos substratos lipídicos en nutrición artificial. En: Nutrición Clínica. Implicaciones del Estrés Oxidativo y de los Alimentos Funcionales. Ed. A Gil Hernandez, MD Ruiz Lopez, A Sastre Gallego y S Schwartz Riera. McGraw-Hill-Interamericana, Madrid.
- Owen, R.W., Giacosa, A., Hull, W.E., Haubner, R., Wurtele, G., Spiegelhalter, B., Bartsch, H. (2000a). Olive oil consumption and health: the possible role of antioxidants. *Lancet Oncol.*, **1**, 107-112.
- Owen, R.W., Giacosa, A., Hull, W.E., Haubner, R., Wurtele, G., Spiegelhalter, B., Bartsch, H. (2000b). The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *Eur. J. Cancer*, **36**, 1235-1247.
- Peters, A.L., Davidson, M.B. (1992). Effects of various enteral feeding products on postprandial blood glucose response in patients with Type 1 Diabetes. *JPEN*, **16**, 69-74.
- Phillips, G.D., Odgers, C.L. (1986). Parenteral and enteral nutrition. Chapt. 10: Lipid. Ed. Churchill Livingstone.
- Rasmussen, O.W., Thomsen, C., Hansen, K.W., Vesterlund, M., Winther, E., Hermansen, K. (1993). Effects on blood pressure, glucose, and lipid levels of a high-monounsaturated fat diet compared with a high-carbohydrate diet in non-insulin-dependent diabetic (NIDDM) subjects. *Diabetes Care*, **16**, 1565-1571.
- Reimer, T., Morlion, B., Fürst, P., *et al.* (2000). Effects of short term parenteral nutrition (TPN) with olive oil lipid emulsion (LE) on antioxidant status of non-septic post operative patients. A comparative, randomized, double-blinded trial. *Clin. Nutr.*, **19**, 1.
- Ros, E. (2003). Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am. J. Clin. Nutr.*, **78**, 617S-625S.
- Sanz-Paris, A., Calvo, L., Guallard, A., Salazar, I., Albero, R. (1998). High-fat versus high-carbohydrate enteral formulae: Effect on blood glucose, C-peptide, and ketones in patients with Type 2 Diabetes treated with insulin or sulphonylurea. *Nutrition*, **14**, 840-845.
- Sax, H.C., Souba, W.W. (1993). Enteral and parenteral feeding. Guidelines and recommendations. *Med. Clin. North Am.*, **77**, 863-880.
- Scaccini, C., Nardini, M., D'Aquino, M., Gentili, V., Di Felice, M., Tomassi, G. (1992). Effects of dietary oils on lipids peroxidation and on antioxidant parameters of rat plasma and lipoprotein fractions. *J. Lipid Res.*, **33**, 627-633.
- Skeie, B., Askanazi, J., Rothkopf, M.M., Rosenbaum, S.H., Kvetan, V., Thomashow, B. (1983). Intravenous fat emulsions and lung function. A review. *Crit. Care Med.*, **16**, 183-194.
- Snyderman, D.R., Murray, S.A., Kornfeld, S.J., Majka, J.A., Ellis, C.A. (1982). Total parenteral nutrition-related infections. *Am. J. Med.*, **73**, 659-671.
- Sturner, W., Kramer, H., Schrezenmeir, J. (1994). Favourable glycaemic effects of a new balanced liquid diet for enteral nutrition. Results of a short term study in 30 type 2 diabetic patients. *Clin. Nutr.*, **13**, 221-227.
- Swiburn, B.A., Boyce, V.L., Bergman, R.N., Howard, B.V., Bogardus, C. (1991). Deterioration in carbohydrate metabolism and lipoprotein changes induced by modern, high fat diet in Pima Indians and Caucasians. *J. Clin. Endocrinol. Metab.*, **73**, 156-165.
- Thomas, B.L., Laine, D.C., Goetz, F.C. (1998). Glucose and insulin response in diabetic subjects: acute effect of carbohydrate level and the addition of soy polysaccharide in defined-formula diets. *Am. J. Clin. Nutr.*, **48**, 1048-1052.
- Tomarelli, R.M. (1988). Suitable fat formulations for infant feeding. In: Dietary Fat Requirement in Health and Development. Ed. J. Beare-rodgers. American. Oil Chemist's Soc. Champaign, IL (USA).

- Venus, B., Smith, R.A., Patel, C., Sandoval, E. (1989). Thermodynamic and gas exchange. Alteration during intralipid infusion in patients with adult respiration distress syndrome. *Chest*, **95**, 1278-1281.
- Visioli, F., Bellosta, S., Galli, C. (1998). Oleuropein, the bitter principle of olives, enhances nitric oxide production by mouse macrophages. *Life Sci.*, **62**, 541-546.
- Visioli, F., Galli, C. (1998). The effect of minor constituents of olive oil on cardiovascular disease: new findings. *Nutr. Rev.*, **56**, 142-147.
- Visioli, F., Petroni, A., Galli, C. (1994). Phenolics compounds extracted from olive oil prevent oxidation of LDL and inhibit platelet function and platelet and leukocyte eicosanoid production in vitro. In: Oxidative processes and antioxidants. Ed. R. Paoletti et al. Raven press. New-York, USA.
- Ythier-Moury, P., Dutot, G., Melin, C. (1990). Modification of biliary secretion associated with parenteral nutrition in the rat: influence of fat emulsion composition. *Clin. Nutr.*, **9**, 26.