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Participation in a Pharmacological Hypolipidaemic Trial Does Not Alter Participants' Dietary Habits

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Summary: Objective: The aim of this study was to observe whether the act of participation in a well-controlled clinical trial can, co-incidentally, modify the dyslipaemic patient's adherence to his/her diet. Design and Subject: Food diaries of 55 men and 51 women (aged 47.4 ± 10.6 and 55.8 ± 12.1 years respectively) were analyzed at the beginning and the end of the double-blind stage of treatment (12 weeks). Statistics: Variance analysis and multi-variant analysis with repeated data by SPSS/PC statistical package. Results: In neither sex were there any statistically significant differences between the start and end of the study with respect to the intake of energy, proteins, total lipids, carbohydrates, saturated fatty acids, polyunsaturated fatty acids, cholesterol, fibre and alcohol. Conclusions: Although in individual cases some changes in dietary awareness can occur, on a larger scale, the hypocholesterolaemic intervention trial induced no significant overall changes in the participants dietary/lifestyle patterns and, as such, augurs well for other such trials in which the effect of the therapy may sometimes be confounded by changes in the patients' life-style patterns coincidental to the act of participation in the trial.

Introduction

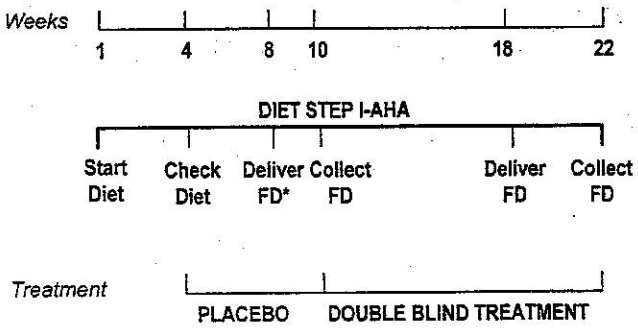
Dietary/life-style factors are major determinants of plasma lipid concentrations [1–6] and, to assess if biochemical changes induced by hypolipidaemic therapy really are the results of the pharmacological agent, it is essential to control for or to quantify accurately the dietary-life-style changes that may occur during the course of the trial [7–9] which may influence an objective assessment of the agent's efficacy. The act of participation in a controlled clinical trial could modify the dyslipaemic patient's dietary awareness and resultant measured biochemical changes could be erroneously attributed to the study medication. A clinical trial involves several medical check-ups over a protracted period together with complementary blood and other biological fluid analyses all of which can result in a heightened sense of the patient's disease susceptibility causing him to change, either as a result of direct counselling or as a result of the desire to please the attending physician, his dietary habits. The converse effect may also occur in that the patient, feeling that the pharmacological agent may be more than sufficient to rectify any imbalance, may chose to ignore dietary advice altogether or to adhere to the recommendations for a short period and then to revert to the previous conditions through lack of motivation [10–12]. Also, the drug itself may spontaneously modify the patient's energy and nutritional demand causing an alteration in eating habits. Hence, the aim of this study was to assess, by analysing the food diaries at the beginning and end of the double-blind treatment phase, if participation itself in the trial affected the patients' adherence to their diet.

Subjects and Methods

Subjects: As part of a large, multi-national, multi-centre, double-blind, randomised trial, 112 patients were recruited from 6 Spanish centres. The patient selection procedure, selection and exclusion criteria, power calculations and trial outcomes are to be reported in detail as and when the trial results have been fully collated and analyzed. Briefly, for the purposes of this report, the subjects, aged between 24 and 73 were recruited from out-patient clinics and who were diagnosed as having primary hypercholesterolaemia with low density lipoprotein (LDL) cholesterol (calculated by the Freidewald formula) of > 160 mg/dl (4 mmol/l) and plasma triglyceride values of < 350 mg/dl (4 mmol/l). All the patients had followed the American Heart Association's step I diet, or equivalent, for at least 4 weeks. Adherence to the diet was checked by the dietitians at the moment the patients were recruited into the study. Excluded from the study were patients with probable Familial Hypercholesterolaemia diagnosed by having a plasma cholesterol > 350 mg/dl (9 mmol/l) together with the presence of tendon xanthomas. Other exclusion criteria were all forms of secondary hyperlipidaemia (including diabetes, hyperthyroidism, liver disease, nephrotic syndrome), patients who had had a coronary bypass graft within the previous six months, or a cerebro-vascular accident, or with cardiac arrhythmias, or heart failure according to the New York Heart Association grade III/IV, or in receipt of any therapy that could alter lipid metabolism such as corticosteroids, immunosuppressants, oral anticoagulants, vitamins containing > 50 mg/day niacin, laxatives and fish oils. All prior lipid-lowering drugs were withdrawn at least one month before the start of the study and, in the case of probucol, a six month wash-out period was considered necessary.

The overall study protocol was in accordance with the terms of the Declaration of Helsinki and was approved by the Clinical Trials Committee of the 6 hospitals participating in the study as well as by the General Directorate of Pharmacy and Health Products of the Spanish Ministry of Health. All patients gave their fully-informed, written consent to participation in the study.

Study design: The overall study was for 22 weeks in (Fig. 1). In the first 4 weeks all study subjects followed the American Heart Association's step I diet and if compliance, assessed by the dietician, was considered good, they were entered into the trial which, for the next six weeks consisted of placebo treatment under single-blind conditions. The remaining 12 weeks consisted of double-blind treatment. During this third period, the patients were randomised into 6 groups: 4 groups were treated with a new 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMGCoA) reductase inhibitor at different doses, 1 group with simvastatin and the other last group with placebo. The patients were rigorously monitored weekly for the next 12 weeks. The recommendations for the diet were kept constant throughout the study and, at each clinical visit, adherence to the diet was evaluated by the dietician.



FD: Food Diaries

Figure 1: Study design.

Dietary Assessments: For standardisation purposes, before commencing the trial all the dietitians and principal investigators in the participating centres received detailed instructions from the nutritionist in the methods of food intake recording. At week 8 (before the start of the treatment phase) the patients were instructed to maintain their food diaries for three days, including one non-working day [13–15] and at week 10 the dietary assessor, in the presence of the patient and aided with photographic dossiers of drinks and foodstuffs which had been weighed or measured previously, quantified the nutritional value of the food consumed. The same procedure was used at the visits in weeks 18 (food diaries delivery) and 22 (food diaries collection and checking).

Nutritional values in terms of energy, proteins, lipids, carbohydrates, fibre, cholesterol, saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs) were quantified according to the Nutrition Co-ordinator Center, Diabetes Forschungsinstitut food composition tables, which enabled differentiation between 671 foodstuffs. A further 55 foods specific to the Spanish diet were incorporated into the analysis.

Data were analysed with the SPSS/PC statistical package. Calculation of values, comparison of mean values and multivariant analysis with repeated data were performed.

Results

Out of 112 patients who were recruited into the dietary assessment at weeks 8 to 10, 6 were excluded at week 22 on the grounds of incomplete dietary recordings leaving 106 completed studies from the 6 different centres in Spain. The distributions with regard to age and sex were comparable: 55 men (aged 47.4 ± 10.6 years) and 51 women (aged 55.8 ± 12.1 years). Table I summarises the energy and nutrient intakes at the beginning of the double-blind treatment phase (week 10) and at the end of this period (week 22). No statistically significant differences were found between the start and end of the study in energy and nutrients, either in men or in women. The percentage variation in intake in men was less than 5% for energy, macronutrients,

Table I: Nutrient intake before (week 10) and the end (week 22) of the treatment period. Values are expressed as means (standard deviations)

	Start	End	Change	%change
		Men (n = 55)		
Energy (kcal/day)	1923 (517)	1871 (535)	–52.4 (402)	2.7
Protein (gm/day)	96.2 (25)	92.3 (29)	–3.9 (26)	4.1
Fat (gm/day)	64.2 (24)	66.7 (26)	2.4 (24)	3.7
Carbohydrate (gm/day)	212 (73)	202 (74)	–10.5 (48)	4.9
Saturated fat (gm/day)	17.1 (6.7)	18.7 (7.9)	1.5 (8.0)	8.7
Polyunsaturated fat (gm/day)	10.8 (7.7)	10.2 (7.6)	–0.7 (7.5)	6.5
Cholesterol (gm/day)	282 (114)	287 (131)	5.9 (139)	2.1
Fiber (gm/day)	17.2 (7.2)	17.2 (7.3)	–0.08 (5.2)	0.5
Alcohol (gm/day)	15.2 (16.2)	13.6 (16.4)	–1.6 (13)	10.5
		Women (n = 51)		
Energy (kcal)	1547 (384)	1506 (390)	–41.0 (409)	2.6
Protein (gm/day)	78.2 (17)	78.0 (18)	–0.2 (19)	0.2
Fat (gm/day)	58.0 (22)	57.3 (24)	–0.7 (26)	1.2
Carbohydrate (gm/day)	177 (49)	169 (47)	–8.2 (52)	4.6
Saturated fat (gm/day)	15.4 (6.2)	15.8 (7.0)	0.4 (8.1)	2.6
Polyunsaturated fat (gm/day)	8.5 (5.3)	7.9 (5.0)	–0.7 (4.8)	8.2
Cholesterol (gm/day)	221 (80)	259 (133)	38.1 (150)	17.2
Fiber (gm/day)	17.0 (5.8)	16.4 (5.9)	0.6 (5.5)	3.5
Alcohol (gm/day)	1.0 (2.7)	1.5 (4.4)	0.6 (2.9)	50

Table II: Nutrient energy intake of the participants during the study compared to the AHA Step One dietary recommendations

%energy supplied by	AHA Step One	Start	End	Start	End
		Men		Women	
Protein	10–20	20.5	20.1	20.7	21.2
Fat	< 30	29.9	31.9	33.0	33.2
– saturated	< 10	8.0	9.0	8.9	9.4
– polyunsaturated		5.0	4.8	4.8	4.6
Carbohydrate	50–60	44.1	43.0	45.8	45.0
Alcohol	≤ 10	5.5	4.9	0.4	0.6

cholesterol and fibre while in women the percentage change was also less than 5% for energy, macronutrients, fibre and SFAs. The largest percentage variation occurred with alcohol. Table II shows the percentage of total daily energy furnished by proteins, lipids, carbohydrates and alcohol as well as SFAs and PUFAs at the start and end of the clinical trial's double-blind treatment phase along with the American Heart Association's Step One recommendations.

The variance analysis comparing the six centres showed no significant differences between them with regard to the estimated energy, proteins, carbohydrates and SFAs supply at each centre.

There were regional differences in the intake of several nutrients (lipids and PUFAs in men and fibre and cholesterol in women) but no significant variations were observed in the pre versus the post treatment values. No significant differences were found with regard to the weight of the patients throughout the study ($p = 0.901$). The mean values were 71.8 ± 11.4, 71.8 ± 11.8 and 71.8 ± 11.6 kg at weeks 4, 10 and 22 respectively.

Discussion

The food diary method used in the present study is easily reproducible and allows acceptable evaluation of the intra-individual variability in food intake. It has been observed that, when the subjects are patients on a specific diet, the reproducibility improves and the intra-individual variability diminishes considerably in com-

parison with people on free-living diets. Furthermore, the fact of keeping the diary over three days (including a non-working day) provides quite an accurate evaluation of intra-individual, day-to-day and inter-weekday variability [13–15].

Differences in data collection between centres was negligible, probably due to the standardized data collection methods. This is evidenced by the fact that no significant differences were observed with regard to the majority of nutrients (energy, proteins, carbohydrates and SFAs) among the different centres. However, significant differences were found between centres with regard to total lipids and fibre which reflect regional differences as reported by the Spanish Ministry of Agriculture [16]. The fact that these differences in food consumption between centres are consistent before and at the end of the study suggests that this is not a confounding factor in this study since the aim was to evaluate if participation in a controlled clinical trial of a hypolipidaemic agent affects the patients' adherence to a dietary regimen.

We observed a remarkable concordance to the dietary recommendations given at the commencement of the study. The general advice to the participants was based on the AHA Step One recommendations and subsequent analysis of the nutrient energy intake showed that the total fat and saturated fat energy intake (30–33% depending on sex) was close to that recommended by the AHA (< 30%) while the percentage of energy supplied by proteins (approximately 20%) was at the upper limit of the recommendations (10–20%). The energy supplied by carbohydrates (ca. 44%) was somewhat lower than that recommended (50–60%). Similar dietary patterns have been reported in studies evaluating nutrient intake in hypercholesterolaemic patients [11, 17].

The patients of our study did not significantly modify their intake of energy and nutrients during the active treatment phase of the controlled clinical trial. In addition, no changes in weight were observed, suggesting that our patients were in energy balance; weight maintenance being an important aspect in assessing the efficacy of a hypocholesterolaemic therapy [7, 11].

In clinical trials in which medical intervention is as intense as it was in this study, it is possible that the patients' adherence to the diet would somehow become modified. Several studies have reported that dietary compliance changes over time in hypercholesterolaemic patients treated with diet alone [11, 18]. The fact that in our study no changes in dietary adherence were observed could be due to several reasons. Firstly, our patients were given dietary recommendations/advice only after their inclusion into the study and after their ability to comply with dietary recommendations had already been sufficiently demonstrated. In contrast, other studies in which changes in dietary compliance were observed, the study design merely involved reminding the subject about the dietary recommendations [11, 18, 19]. Secondly, the study period was relatively short (12 weeks) whereas modifications in dietary compliance appear to occur in studies conducted over more protracted periods lasting up to several years [11, 18]. Lastly, the patients in the present clinical trial were volunteers who were aware of the possibly debilitating nature of their clinical condition and, given the opportunity of intensive clinical monitoring, made them more receptive/motivated towards compliance. In support of this are the observations [18–20] that patients with an elevated risk-factor status for cardiovascular disease, once they have been made aware of it, follow dietary recommendations much more rigorously than those in whom the disease has not yet manifested itself.

In conclusion, in the present study with hypercholesterolaemic patients, no significant changes in the adherence to diet were observed during the period of intensive hypolipidaemic therapy. Finding no significant changes in dietary intake in this type of clinical trial is of considerable importance since it is, then, clear that any plasma constituent changes observed are due to the medication and not to any variation in dietary habit.

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References

1. Grundy, S.M. and Denke, M.A. (1990) Dietary influences on serum lipids and lipoproteins. J. Lipid. Res. *31,* 1149–1172.
2. Connor, W.E. and Connor, S.L. (1993) Importance of diet in the treatment of familial hypercholesterolemia. Am. J. Cardiol. *72,* 42D–53D.
3. Masana, L.L., Camprubí, M., Sardà, P., Solà, R., Joven, J. and Turner, R. (1991) The Mediterranean-type diet: is there a need for further modification? Am. J. Clin. Nutr. *53,* 886–889.
4. Joven, J., Vilella, E., Masana, L. and Ansoleaga, J. (1991) Low density lipoprotein receptor levels and response to dietary and pharmacological intervention in polygenic hypercholesterolemia. Clin. Chimi. Acta *197,* 67–76.
5. Groth, K., Kirk, M. and Alvin, B. (1991) Immediate and sustained reduction in serum cholesterol achieved in 4-week Heart Tune program. J. Am. Diet. Assoc. *91,* 1100–1103.
6. Gotto, A.M. Therapeutic intervention for hypercholesterolemia. Clin. Cardiol. *15* (3), 18–21.
7. Goff, D.C., Shekelle, R.B., Moyé, L.A., Katan, M.B., Gotto, A.M. and Stamler, J. (1993) Does body fatness modify the effect of dietary cholestered on serum cholesterol? Results from the Chicago Western Electric Study. Am. J. Epidemiol. *137,* 171–177.
8. Leighton, R.F., Repka, F.J., Birk, Tj. *et al* (1990) The Toledo exercice and diet study. Arch. Inter. Med. *150,* 1016–1020.
9. Fodor, J.G. and Chockalingam, J. (1991) Modification of cardiovascular risk factors in rural population of Newfoundland through nutritional counselling. Cor. Vasa. *33* (2), 107–113.
10. Koletzo, B., Kupke, I. and Wendel, U. (1992) Treatment of hypercholesterolemia in children and adolescents. Acta Paediatr. *81,* 682–685.
11. Bloemberg, B.P.M., Kromhout, D., Goddijn, H.E., Jansen, A. and Oberman-de Boer, G.L. (1991) The impact of the guidelines for a healthy diet of the Netherlands Nutrition Council on total and high density lipoprotein cholesterol in hypercholesterolemic free-living men. Am. J. Epidemiol. *134,* 39–48.
12. Denke, M.A. and Frantz, I.D. (1993) Response to a Cholesterol-Lowering diet: Efficacy is greater in hypercholesterolemic subjects even after adjustment for regression to the mean. Am. J. Med. *94,* 626–631.
13. Witschi, J.C. (1990) Short-term dietary recall and recording methods. In: Nutritional Epidemiology (Willett, W., ed.), pp. 52–68, Oxford University Press, New York.
14. Marr, J.W. (1971) Individual dietary surveys: Purposes and methods. Word Rev. Nutr. Diet. *13,* 105–164.
15. Hercberg, S. and Galán, P. (1985) Méthodes d'evaluation de l'état nutritional des populations: In: Nutrition et Santé Publique. Approche épidemiologique et politiques de prévention (Hercberg, S., Dupin, H., Papoz, L., Galán, P., eds.), pp. 75–98, Lavoisier, Paris.
16. Ministerio de Agricultura, Pesca y Alimentación. (1995) La alimentación en España, pp. 1–433, Ministerio de Agricultura, Pesca y Alimentación, Madrid.
17. Demark-Wahnefried, W., Bowering, J. and Cohen, P.S. (1990) Reduced serum cholesterol with dietary change using fat-modified and oat bran supplemented diets. J. Am. Diet. Assoc. *90,* 223–229.
18. Chima, C.S., Miller-Kovach, K., Zeller, M., Cook, K. and Schupp, K. (1990) Lipid management clinic: Dietary intervention for patients with hypercholesterolemia. J. Am. Diet. Assoc. *90,* 272–274.
19. Dobs, A.S., Sarna, P.S. and Wilder, L. (1991) Lipid-lowering diets in patients taking pravastatin, a new HMG-CoA reductase inhibitor: compliance and adequacy. Am. J. Clin. Nutr. *54,* 696–700.
20. McMurry, M.P., Hopkins, P.N., Gould, R. *et al* (1991) Family-oriented nutrition intervention for a lipid clinic population. J. Am. Diet. Assoc. *91,* 57–65.

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