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Effect of quantitative and qualitative diet prescription on children behavior after diagnosis of heterozygous familial hypercholesterolemia☆

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ABSTRACT

Background: Diet and healthy modifications in lifestyle represent the first therapeutic approach for early intervention in hypercholesterolemia. We aimed to evaluate the impact of a qualitative dietetic program rather than a quantitative one on metabolic parameters and anxiety level of children affected by heterozygous familial hypercholesterolemia [heFH] and their mothers.

Methods: In a sample of 42 heFH normal weight children (11.4 ± 2.9 years old), we investigated the factors which were associated with children perceived quality of life and with their mothers' anxiety levels after qualitative dietary changes rather than after quantitative ones.

Results: The administered diets had similar metabolic effects. However, higher Child Behavior Checklist (Behavior Problems subscale) [CBCL] scores were significantly associated with the permanence in quantitative diet, as well as children's higher age, higher Children's Depression Inventory 2 [CDI2] and State–Trait Anxiety Inventory for Children [STAI-CH] score, and with mothers' anxiety at the baseline.

Conclusion: In heFH children, an intervention in the diet to improve food choice seems to be associated with a more healthy children behavior rather than a quantitative diet.

1. Introduction

Familial Hypercholesterolemia [FH] and the other severe forms of familial dyslipidemia showing a clear phenotype during the infancy are well-known associated with a variable though significant increase in developing atherosclerosis early clinical manifestations [1,2]. For this reason, the latest European Atherosclerosis Society Consensus Panel emphasizes the importance of the early lipid-lowering treatment initiation, for a greater long-term benefit later in life [3].

Such as for adults, children diet and healthy modifications in lifestyle represent the first therapeutic approach for early intervention in FH [4]. To date, there is a strong evidence showing that dietary factors are able to influence atherogenesis directly and interacting with the other traditional cardiovascular [CV] risk factors [5]. However, ᶜhildren compliance to quantitative dietary modifications tends to be relatively poor and largely depending on their parents' education and family background. Furthermore, stringent diet modifications often exert a negative impact on children perception on quality of life [6]. On the opposite, qualitative dietary suggestions are, in general, better accepted and usually do not cause weight loss, which is likely to be definitely unfavorable in normal weight children because of the growth process [7,8].

In this pilot clinical study, we aimed to evaluate the effect of a qualitative or a quantitative lipid-lowering dietary program on the metabolic parameters and anxiety level of 42 children affected by heterozygous familial hypercholesterolemia [heFH] and their mothers.

2. Methods

2.1. Study design

We consecutively evaluated 42 normal weight children, 22 males and 20 females, mean age 11.4 ± 2.9 years old (range: 6–17 years) firstly diagnosed for FH in the setting of a specialized ambulatory service for dyslipidemia diagnosis and management [9]. The heHF diagnosis was based on the Dutch Lipid Clinic Network [DLCN] criteria [10], which consists of a point score system and includes information about personal and first-degree relatives with high LDL-C, tendon xanthomas, and premature coronary artery disease. Definitive FH scores was defined as >8 points, probable 6–8, possible 3–5, and unlikely <3. Owing to the small number of patients with definitive and probably FH, these two groups were combined as one "definitive/probable" and patients were considered for the study.

A trained nutritionist prescribed children a standard qualitative dietary scheme adherent to the Mediterranean diet. At 3-month follow-up, those children continuing to have suboptimal LDL values (defined as >130 mg/dL [3]; 40 children out of 42), have been then recommended to switch to a quantitative dietary scheme. However, as expected from our routine practice, some of their parents (21/40) objected because of the management difficulties (i.e. daily energy intake count, food weighing) that this type of approach would have implied. When this occurred, we systematically planned to recommend the parents to intensify the previously prescribed qualitative dietary scheme.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Consequently, based on the parents' preference, patients were assigned to get an individualized quantitative diet or an intensification of the qualitative diet, both aimed to reduce the global cardiovascular disease risk and in particular plasma cholesterol levels.

2.2. Psychometric assessment

At the beginning and every 3 months thereafter, a child psychologist administered the Child Behavior Checklist [CBCL] [11], the Children's Depression Inventory 2 [CDI2] [12] and the State–Trait Anxiety Inventory for Children [STAI-CH] [13] to the patients, and the Symptom Checklist-90-R [SCL-90-R] to their mothers. All subjects were adequately instructed to respond to the items and were motivated in order to cooperate with the investigators.

The CBCL, CDI2 and STAI-CH reliability and validity have already been well-established in several studies using a variety of different techniques [14–16]. Moreover, they have recognized good psychometric properties.

CBCL had previously been used in research involving hyperlipidemic children [17–19]. The school-age version of the CBCL (CBCL/6–18) provides ranging for 20 competence and 118 problem behavior items. For the purpose of the present pilot study, however, we used only the latter ones, which have better validity [20] and was able to evaluate the most relevant disturbances for the subjects. CBCL uses age and gender normative data to create standard scores, which are scaled so that 50 is average for the youth's age and gender, with a normal deviation of 10 points. CBCL's scores can be interpreted as falling in the normal (<93th percentile), borderline (93–97th percentile) or clinical behavior (>97th percentile).

The CDI2 is a 27-item self-rated depression scale being widely used and accepted assessment for the severity of depressive symptoms in children. Each CDI2's statement is identified with a rating from 0 to 2, and 6 to 16 aged healthy children were demonstrated to reach mean scores ranging from 8.29 to 9.72 [21,22].

The STAI-CH is a self-report anxiety inventory for upper elementary or junior high school aged children, consisting of two separate 20-item 3-point rating scales for measuring trait and state anxiety. The State-Anxiety scale assesses the current level of anxiety at the examination, while the Trait-Anxiety scale measures the anxiety general level. They are both verbally administered and usually do not require special instructions or prompting. Normative data indicate mean STAI-CH state scores of 30–37 for boys and 30–38 for girls [23].

As regards mothers, psychological symptoms were evaluated by the SCL-90-R, which assesses depression, anxiety and other dimensions of negative emotions (such as hostility, somatization, paranoid ideation, interpersonal sensitivity, obsessive-compulsive behavior and psychoticism) [24]. A high number of studies have been conducted demonstrating the reliability, validity and utility of the instrument, which is actually one of the most widely used measure of psychological distress in clinical practice and research. The purpose of our study was focusing on items related to depression and anxiety. Raw scores for each dimension were converted into standardized T-scores (mean, 50 points; SD, 10 points) based on gender-appropriate non-patient norms. Thus, a T-score of 60 placed a participant in the 84th percentile of the normative sample, regardless of symptom dimension [24].

Mothers were also asked to quantify the health risk perception of ones' families and children with a 10-point visual analogue scale.

2.3. Physical evaluation

Height and weight were measured respectively to the nearest 0.1 cm and 0.1 Kg. Body mass index [BMI] was calculated as body weight in kilograms, divided by height squared in meters (Kg/m^2). The BMI values were reported on the appropriate growth corves [25].

2.4. Laboratory analysis

At each visit, a 12-hour fasting blood sample was taken. Hematochemistry analyses were evaluated according to standardized methods by trained personnel, and included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), lipoprotein (a) (Lp(a)), and fasting plasma glucose (FPG). Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula [26].

2.5. Dietary assessment

In order to evaluate the compliance to the dietary instructions, patients and their families were asked to fill weekly food diaries at baseline and at each control visit thereafter. A nutritionist provided detailed instruction to children and their parents for correctly record food intake, and subsequently analyzed the diaries. The nutritional evaluation was performed with Software MètaDieta® (Me.Te.Da S.r.l., San Benedetto del Tronto, Italy), using Italian Food Composition databases.

Parents signed an informed consent. The study was carried out in accordance with the declaration of Helsinki and approved by the local ethical board.

2.6. Statistical analysis

Data were analyzed using intention to treat by means of Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corporation, Armonk, New York, USA) for Windows. The normal distribution of the tested parameters was evaluated by the Kolmogorov-Smirnov test. The baseline characteristics of the sample were described by the independent *t*-test and the Chi-square test, followed by Fisher's exact test for categorical variables. Every continuous parameter was compared by repeated-measures analysis of variance (ANOVA). The intervention effects were adjusted for all the considered potential confounders by the analysis of covariance (ANCOVA). ANOVA was performed to assess the significance within and between the intervention groups. The statistical significance of the independent effects of the interventions on the other variables was determined using ANCOVA. A one-sample *t*-test was used to compare the values obtained before and after the treatment administration; 2-sample t-test was used for between-group comparison. All the descriptive values were expressed as mean ± standard deviation [SD] or number and percentage and every test was two-tailed. Then, a logistic regression analysis was carried out in order to detect which factors were independently associated with higher CBCL/6–18 score. The risk estimate for higher CBCL/6–18 score was calculated and expressed as odds ratio [OR] and 95% confidence interval [95% CI]. For comparison, we provide the crude effect estimate, as well as the covariate-adjusted effect by age-range and sex. A p-value <0.05 was always regarded as statistically significant.

3. Results

During the first phase of the study, all dietary components improved versus baseline (Table 1). Two children achieved the desired LDL-C level (<130 mg/dL) and were no longer considered for the purpose of the study. After this period, the intervention groups were well matched for all the considered variables at baseline (Table 2).

The positive metabolic impact observed after the Mediterranean diet phase was maintained during both following dietary programs, though it did not improve further. However, children undergone the quantitative dietary program experienced a decrease in BMI (Table 2).

After the first 3-month Mediterranean diet period, the probability of getting a higher CBCL score than the median in population –which was of 62 points- was 2.4 times higher for children aged 10–14 years and significantly lower in female children rather than males (Table 3). Furthermore, getting higher CBCL score was 8-time easier for subjects with a moderate-high CDI score, and 4-time easier for those with high STAIC score or the more anxious mothers (Table 3).

After assignment to the different dietary approaches, the probability to have a high CBCL score was 5 times higher in subjects assigned to the quantitative diet, than in the ones assigned to continue the qualitative one. Male sex and ranging 10–14 years old were other determinants of higher CBCL score (Table 3). Moreover, getting higher CBCL score was 5-time more likely for subjects with a moderate-high CDI score and 3-time more likely for the ones with a high STAIC score or the more anxious mothers (Table 3).

Mothers' risk perception related to their children cardiovascular health was significantly related to a positive family history for early cardiovascular disease (OR 4.9, 95% CI 1.5–7.9), a positive family history for late cardiovascular disease (OR 3.7, 95% CI 1.3–6.5), a family history positive for hyperlipoproteinemia (OR 3.1, 95% CI 1.2–6.1), high food quantity (OR 2.8, 95% CI 1.1–5.5), high child LDL-C level (OR 2.6, 95% CI 1.1–5.3), high child TG level (OR 2.3, 95% CI 1.0–4.9). However, the risk perception was not significantly associated to poor food choices (OR 1.4, 95% CI 0.7–2.5), low child HDL-C level (OR 0.9, 95% CI 0.6–2.3), child sedentary (OR 0.6, 95% CI 0.4–1.1), and passive smoking (OR 0.3, 95% CI 0.1–1.1).

At the end of the dietary intervention period, 32 patients out of 40 began statin treatment, as per current guidelines.

4. Discussion

In clinical practice, dietary counseling is always necessary but also time-consuming and the results are often not satisfying, especially when patient compliance is not adequate [27].

The present findings are in line with what Delahanty and colleagues observed in adults, showing that a dietary program based on quality of food choice is associated with an improved perceived quality of life [28]. Furthermore, the loss of weight experienced during the quantitative dietary program could be potentially harmful to the growth process of the children in the long term, as they were normal weight at baseline [29]. On the other side, a more intensive lipid reduction in diet seems not

Table 1
Changes in BMI, main dietary component intakes, and laboratory parameters after 3-month Mediterranean diet.

	Baseline	3-Month Mediterranean diet
Parameters		
BMI (Kg/m^2)	20.1 ± 3.2	18.9 ± 3.5
Fasting plasma glucose (mg/dL)	87 ± 14	83 ± 8
Total cholesterol (mg/dL)	284 ± 22	251 ± 16*
LDL-cholesterol (mg/dL)	191 ± 23	161 ± 20*
Triglycerides (mg/dL)	201 ± 28	164 ± 17*
HDL-cholesterol (mg/dL)	54 ± 9	56 ± 10
Non-HDL-cholesterol (mg/dL)	230 ± 21	195 ± 18*
VLDL-cholesterol (mg/dL)	40 ± 6	33 ± 5*
Lipoprotein (a) (mg/dL)	21 ± 3	20 ± 4
Dietary component intake		
Energy (MJ)	7.58 ± 1.15	6.99 ± 0.98*
Total fat (% energy)	26.1 ± 3.0	24.3 ± 3.2*
Saturated fat (%)	9.8 ± 1.6	8.1 ± 1.8*
Monounsaturated fat (%)	7.6 ± 2.1	8.6 ± 1.9*
Polyunsaturated fat (%)	4.3 ± 1.4	5.1 ± 1.3
Cholesterol (mg)	324 ± 12	228 ± 18*
Protein (%)	14.3 ± 1.6	15.1 ± 1.9
Carbohydrate (%)	59.4 ± 5.2	60.3 ± 6.4
High glycemic index carbohydrate (% on all carbohydrates)	21.8 ± 4.2	12.4 ± 2.9*

* $p < 0.05$ compared with the baseline.

Table 3
Crude and adjusted risk for high CBCL/6–18 score >62 at the end of the observation period.

	% with high CBCL/6–18 score	OR (95% CI)	
		Crude	Adjusted
Study phase			
Mediterranean diet	42.8	1.0	1.0
Strictly lipid-lowering qualitative diet	43.1	1.1 (0.2–2.1)	1.2 (0.3–2.6)
Quantitative diet	72.0	3.4 (1.0–5.2)	4.9 (1.9–11.6)
Age of child (years)			
6–9	32.2	1.0	
10–14	41.2	1.5 (1.0–2.8)	
15–17	49.6	1.7 (0.9–3.9)	
Sex			
Male	46.6	1.0	
Female	39.9	0.8 (0.3–0.9)	
CDI2 score at 3 months			
0–3	27.2	1.0	1.0
4–7	54.3	2.1 (1.1–3.4)	5.3 (2.0–18.5)
8–23	59.8	2.7 (1.2–7.9)	6.6 (1.9–14.8)
STAI-CH score at 3 months			
20–29	26.8	1.0	1.0
30–37	39.4	1.5 (0–8-2.5)	1.7 (0.9–2.8)
38–63	62.3	2.7 (1.0–7.1)	3.2 (1.1–7.6)
Mother anxiety at the baseline			
SCL-90-R < 50	35.2	1.0	1.0
SCL-90-R > 50	69.9	2.5 (1.3–4.9)	3.4 (1.7–6.1)
Mother depression at the baseline			
SCL-90-R < 50	34.7	1.0	1.0
SCL-90-R > 50	39.6	1.2 (0.8–2.5)	1.3 (0.9–3.1)

Adjusted for age and sex of the child and mother's age and education level.

to be associated with a clinically significant improvement in plasma lipid levels [30].

Certainly, this study produces new knowledge in a relatively unexplored area of preventive pediatric care, obtained by the application of validated psychometric scores [14–16]. However, it is not without limitations. The main one is the relatively small sample size, but compatible with the disease epidemiology in children age. Secondly, this is not a randomized clinical study, since the patients were assigned to the different intervention groups based on the parent preference. However,

Table 2
Changes in BMI, main dietary component intakes, and laboratory parameters after diet intensification.

	Mediterranean diet (n = 21)	3-Month strictly lipid-lowering qualitative diet (n = 21)	Mediterranean diet (n = 19)	3-Month quantitative diet (n = 19)
Parameters				
BMI (Kg/m^2)	18.2 ± 3.6	19.1 ± 3.1	19.1 ± 3.4	18.6 ± 2.8*
Fasting plasma glucose (mg/dL)	87 ± 6	84 ± 10	81 ± 9	82 ± 9
Total cholesterol (mg/dL)	250 ± 19	254 ± 15	254 ± 13	249 ± 11
LDL-cholesterol (mg/dL)	166 ± 18	164 ± 24	163 ± 19	167 ± 18
Triglycerides (mg/dL)	161 ± 19	166 ± 18	166 ± 23	158 ± 13
HDL-cholesterol (mg/dL)	52 ± 11	55 ± 11	58 ± 8	51 ± 7
Non-HDL-cholesterol (mg/dL)	198 ± 15	199 ± 18	196 ± 20	198 ± 15
VLDL-cholesterol (mg/dL)	32 ± 6	33 ± 6	35 ± 3	32 ± 4
Lipoprotein(a) (mg/dL)	17 ± 6	21 ± 3	22 ± 3	21 ± 4
Dietary component intake				
Energy (MJ)	7 ± 0.92	7.12 ± 0.67	6.99 ± 0.98	6.45 ± 0.78
Total fat (% energy)	22.4 ± 4.2	24.5 ± 3.4	24.3 ± 3.2	22.9 ± 5.1
Saturated fat (%)	7.6 ± 2.8	8.2 ± 1.9	8.2 ± 1.9	7.8 ± 1.4
Monounsaturated fat (%)	7.8 ± 1.3	8.5 ± 1.8	9.1 ± 0.8	8.8 ± 1.4
Polyunsaturated fat (%)	5.4 ± 1.2	4.9 ± 1.4	4.8 ± 1.4	5.2 ± 1.2
Cholesterol (mg)	221 ± 17	232 ± 19	230 ± 15	198 ± 21
Protein (%)	14.9 ± 1.7	14.9 ± 2.2	15.6 ± 2.3	15.9 ± 1.8
Carbohydrate (%)	60.7 ± 6.4	60.1 ± 7.2	60.4 ± 6.1	60.6 ± 4.4
High glycemic index carbohydrate (% on all carbohydrates)	12.5 ± 2.4	12.9 ± 3.2	12.3 ± 2.7	14.5 ± 3.3

* $p < 0.05$ vs. standard Mediterranean diet.

this allowed us to reach a priori a high compliance to the dietary intervention. Finally, the quantitative phase effect was determined after the qualitative one. This was necessary to let the patients adapt to the diet in a less traumatic way. Certainly, it could have reduced the negative impact of the quantitative diet or increased the qualitative one in the second part of the study. However, we have reasons to think that it does not reduce the value of our conclusions because of the large difference observed between the dietetic approaches.

If confirmed by larger randomized controlled clinical trials, the practical application of our finding is that an easier, less time-consuming general suggestion on dietary pattern improvement could induce less psychological stress in young heFH patients than a detailed quantitative prescription of dietary components. This could have also some relevance on long-term patient compliance.

5. Conclusion

In conclusion, in children with heFH a dietary program based on quality of food choice is associated to a more healthy children behavior than a quantitative diet. However, the result is particularly influenced from the baseline mother anxiety level.

Authors' contributions

AFGC clinically managed the patients, analyzed the data and wrote the article; FF wrote the article; MG, MB and GD clinically managed the patients; CB critically revised the article. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare not to have any conflict of interest in the publication of the present work.

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