Improvement of Inflammation and Pain After Three Months' Exclusion Diet in Rheumatoid Arthritis Patients

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Research article

Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease affecting the synovial joints and causing severe disability. Environmental and lifestyle factors, including diet, have been proposed to play a role in the onset and severity of RA. Dietary manipulation may help, to manage the symptoms of RA, by lowering inflammation, and potentially decreasing pain.

Methods: In 40 patients with long standing RA, with stable symptoms, and treated with conventional (c-) and biological (b-) Disease modifying anti-rheumatic drugs (DMARDs), the effect of 3-months' diet avoiding meat, gluten, and lactose (privative diet) was evaluated in comparison with a control balanced diet including those foods. Patients choosing the exclusion diet were followed in parallel to an equal number of patients on their normal diet, and RA was clinically assessed at Time 0 (T0), through the Visual Analogue Scale (VAS), for pain, and the Disease Activity Score of 28 joints (DAS 28) for RA activity. Patients were also administered the Short Form Health survey (SF-36) and the Health Assessment Questionnaire (HAQ). At T0 a blood sample was collected for laboratory tests, and anthropometric measurements were recorded. These evaluations were repeated at the end of the 3 months'dietary regimens.

Results: A significant decrease in VAS and the improvement of the overall state of physical and mental health, assessed through SF-36, was observed in patients following the avoidance diet. Both dietary regimens resulted in the improvement of quality of life compared to baseline values, however the change was significant only for the exclusion diet. With either diet, patients showed significant decreases of body weight and body mass index (BMI), with a reduction of waist and hips circumferences, lower basal glucose and circulating leptin levels. Exclusion diet was also able to significantly reduce systolic (SYS) (p=0.002) and diastolic (DIA) (p=0.027) arterial pressure. The number of circulating leukocytes and neutrophils, and the level of hs-C-Reactive Protein (CRP) were also significantly decreased after 3 months of the meat-, lactose, and gluten-free diet.

Conclusions: Our results suggest that an exclusion diet can result in a better control of inflammation and pain in RA patients under stable optimized drug treatment.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease typically affecting the synovial joints, in which autoimmunity drives dysregulated proinflammatory cytokines secretion[1]. If not properly managed, RA leads to severe disability in most patients[2]. The increase in the incidence of autoimmune diseases observed in developed countries, has been associated with the decrease in infectious load, and the dramatic changes in environmental and lifestyle factors, and particularly the diet, which affects the composition of the gut microbiota[3, 4]. These factors, and the diet, have been postulated to play a role in the expression and severity of RA[5, 6].

A decrease in dietary fibers and an increase of fat and sugar intake, which is typical in Western diets, contribute to chronic low-grade inflammation and gut microbial dysbiosis[7–9]. These changes promote immune dysfunction which is pivotal to the pathogenesis of RA[10–12]. More importantly, they are amenable to correction through an appropriate diet.

Dietary manipulations have been used to manage the symptoms of RA,[13–15] increasing antioxidant levels and altering lipid profile, and potentially modifying the intestinal flora[5, 14, 15].

Nutritional interventions reporting subjective beneficial effects[16] have been popularized and adopted by many patients. In this regard, consumption of red meat[17, 18], dairy products or specifically lactose[19, 20], and more recently gluten[21], have been indicted as possible causes of arthritis or of its exacerbations. The effects of avoiding such foods may depend on generation of the choline metabolite trimethylamine N-oxide (TMAO), an inflammation promoting substance implicated in autoimmune diseases[22].

In this study, we evaluated the effect of a diet deprived of meat, gluten and lactose, in patients with long-standing well-controlled RA, in comparison with a normal balanced diet including those items, followed for three months. The main endpoints of our study were the assessment of disease activity, pain perception, and modifications of quality of life in RA patients. Several inflammatory and anthropometric measurements were also recorded before and after the diet.

2. Materials And Methods

2.1. Patients enrollment

A total of 40 patients with RA, fulfilling the classification criteria of the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR)[23], were among those attending the Rheumatology Clinic of the hospital "SS. Annunziata" in Chieti. All were females with age range between 31 and 72 years (mean age ± SEM 52.23 ± 1.61), and all had been treated with the same optimized therapy for at least one year, consisting in a combination of biological (b-) and conventional (c-) Disease Modifying Antirheumatic drugs (DMARD) (n = 7); or monotherapy with a biological drug (n = 22), or c-DMARDs only (n = 11), showing stable disease activity, assessed with the scales described below.

Comorbidities (diabetes, dyslipidemia, celiac disease), treatment with medium to high doses of corticosteroids, and current or previous dietary regimens with avoidance of meat, gluten or milk, represented exclusion criteria. Moreover, patients were asked about important lifestyle changes (significant increase in physical activity, job change, etc.) which did not occur in the previous year.

Low-dose steroid therapy and occasional use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or analgesics were allowed throughout the study.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Provinces of Chieti and Pescara and the University of Chieti-Pescara (*Comitato Etico delle Province di Chieti e Pescara e dell'Universita' degli Studi "G. d'Annunzio" di Chieti-Pescara* Project no. 10/20).

2.2. Study design and dietary regimens protocol

Selected patients were 20 RA patients who expressed the intention to start a diet avoiding all meat, gluten and lactose, and accepted to do so with the approval of expert dieticians, and 20 consecutive RA cases matching the previous ones. asked to follow their usual diet including meat, gluten and lactose, and approved by expert dieticians (balanced diet- B). No changes in daily habits or treatment were required. The study was deemed observational. The age groups of patients on either diet were not different (mean ± SEM: 50.60 ± 2.24 years for those on avoidance diet, and 54.10 ± 2.09 years for those on their normal diet; p = 0.269).

Diets were supervised by expert physicians at the Obesity Center of the "SS. Annunziata" hospital in Chieti; both diets gave an intake of about 1500 Kilocalories (Kcal)/die, and were optimized according to current guidelines for balanced composition in macronutrients[24], daily intake of cholesterol (< 300 mg/die), saturated fatty acids (< 10% of total energy intake)[25], oligosaccharides (< 15% of total energy intake), and dietary fiber (25–30 g/die)[26]. Moreover, for both types of diet the total protein intake was 50% from animal and 50% from vegetable proteins.

The macronutrient composition of the meat-, gluten-, and lactose-deprived diet was as follows: 56% of total Kcal from carbohydrates, 16% from proteins and 28% from fat. The main contributors to protein intake were fish (50.1%) for animal protein and flour products (16.1%), legumes (19.3%), fruit and vegetables (14.5%) for vegetable protein. The macronutrient composition of the balanced diet was as follows: 56% carbohydrates, 17% proteins, 27% fats. The main contributors to protein intake were meat (28.8%), milk (products) (7.1%), for animal protein and flour products (31.1%), legumes (15.7%), fruit and vegetables (17.3%) for vegetable protein.

2.3. Disease monitoring

At the start of the observation, Time 0 (T0), all patients underwent clinical evaluation of RA through an objective physical articular examination, used also to calculate the Disease Activity Score of 28 joints (DAS 28) score (see below). The Visual Analogue Scale (VAS) was used for pain assessment, asking the patient to locate on a 100 mm line, the point that best identified the intensity of pain, in the previous week (where 0 represents no pain and 100mm represents the maximal pain perceived)[27]. Patients were also asked how the disease condition affected their quality of life, by administration of the Short Form Health survey (SF-36)[28] and the Health Assessment Questionnaire (HAQ)[29]. The activity of RA was evaluated by the 4-parameters DAS 28 using ESR[30].

All the above described measures were repeated, after 3 months of diet (T1) in both groups.

2.4. Laboratory data and anthropometric measurements

Patients underwent blood samples collection at T0 by venipuncture, and a complete blood count, and clinical chemistry tests were performed, including Oral Glucose Tolerance Test (OGTT), Homeostasis Model Assessment (HOMA) index, insulin level, serum lipid profile, Erythrocyte Sedimentation Rate (ESR), high-sensitivity C-Reactive Protein (hs-CRP), transaminase levels, total proteins, albumin, and transferrin. Serum aliquots, obtained after blood clotting and centrifugation, was stored at − 80°C, until assayed for circulating cytokines and adipokines evaluation. Anthropometric measurements, patients' height, weight and calculation of the Body Mass Index (BMI) (kg/m^2), arterial blood pressure and Bioimpedance Analysis (BIA)[31] were also recorded. BIA parameters were: muscle mass, fat mass, bone mass, water, and basal metabolism. All the above described evaluations obtained at T0 were repeated after 3 months of deprived (group A) or balanced (group B) diet.

2.5. Detection of adipokines and cytokines

Selected cytokines and adipokines were measured using specific Quantikine® ELISA kits (Human Leptin Immunoassay, Human Adiponectin Immunoassay, Human TNFα Immunoassay, Human IL-10 Immunoassay, and Human INFγ Immunoassay) purchased from R&D Systems (Minneapolis, MN). All ELISA assays were performed on serum samples collected at T0 and T1, in the same batch, following the manufacturer's instructions.

2.6. Statistical analysis

Data were reported as mean and standard error of mean (SEM). Nonparametric statistics was used to compare the subjects at T0, and after the dietary intervention (Wilcoxon matched-pairs signed-rank test) and to compare the patients belonging to group A or B, at T0 (Mann-Whitney t-test). Spearman's rank correlation coefficient was calculated to assess the relationship between the variables changes at T1 vs T0. The threshold of statistical significance was set at p = 0.05. Data analysis was performed on GraphPad Prism 6 Software, version 6.01, 2012.

3. Results

3.1. Patients' adherence

A total of 12 patients withdrew from the study before T1, and this left 15 cases in group A, and 13 in group B. Causes of poor compliance were difficulties to adhere to diet(s) in 9 patients (75%), and nonspecific gastrointestinal complaints in 3 patients (25%).

3.2. VAS score

To evaluate the pain perception and its changes with dietary regimen, the VAS score was used (Fig. 1). In group A, a significant decrease in VAS was found after the diet (T0 mean ± SEM: 54.52 ± 5.22; T1 mean ±

SEM: 38.38 ± 5.26; p < 0.003). In group B, with the control diet, the VAS score also decreased, but not significantly.

3.3. DAS 28 score

The composite clinimetric index DAS 28 was used to evaluate changes in RA activity after 3 months of diet (Fig. 2). The DAS 28 score was not significantly different before and after either diet; a non-significant lower mean value was recorded in group B, and a small increase was measured after 3 months. The opposite change was observed in group A.

3.4. SF-36 score

Figure 3 summarizes the 8 scales included in the SF-36 questionnaire, showing the overall state of physical and mental health in patients at the beginning (T0) and after 3 months' diet (T1). Note that higher values indicate a better health status. In group A, the T1 score (mean ± SEM: 60.03 ± 4.83) was significantly increased (p < 0.001) with respect to T0 values (mean ± SEM: 44.88 ± 5.41), whereas in group B no significant change was detected.

When the 8 items of the SF-36 questionnaire were considered apart, in group A we observed a significant increase for the state of health (SH), the vitality (V), the social activities (SA), and the role limitations due to the emotional state (RE) scores (Fig. 4). In group A, the increase of V score was inversely correlated with pain reduction, assessed by the VAS (rho=-0.546, p = 0.027). In group B, the increase of the 8 items of SF-36, with respect to T0, were smaller and did not reach statistical significance, with SH, V, and mental health (MH) scores showing no variations respect to T0.

3.5. HAQ score

Items on the patient's physical, psychological, and social dimensions, in the HAQ test, are organized so that a lower score indicates a better quality of life. Both the deprived and the balanced diet were associated with improved quality of life in RA patients compared to baseline, however the difference reached significance (p < 0.05) only for patients belonging to the group A (Fig. 5).

3.6. Anthropometric measures

The anthropometric measures are reported in Table 1. Patients following the two diet regimens were not significantly different at T0 for all the variables considered (see last column). After 3 months of the two diets, patients showed a significant decrease of body weight and BMI (Table 1). Both dietary regimes were also significantly effective in reducing waist and hips circumference. Interestingly, in group A, a significant reduction of systolic (SYS) (p = 0.002) and diastolic (DIA) (p = 0.027) arterial pressure was achieved, but this did not occur in group B. Among the BIA parameters, no change in muscle mass and basal metabolic rate was observed after diet in either group, whereas fat mass was significantly reduced in both.

Table 1
Anthropometric measures of recruited patients in groups A and B

	group A (n = 15)		*p-value*[a]	group B (n = 13)		*p-value*[a]	*p-value*[b]
	T0	T1		T0	T1		
Weight (Kg)	79.31 ± 3.96	72.87 ± 2.85	< 0.001	72.68 ± 3.02	69.53 ± 3.13	0.004	*0.205*
BMI (kg/m2)	31.77 ± 1.77	29.04 ± 1.29	< 0.001	29.50 ± 1.46	28.33 ± 1.44	0.010	*0.341*
BIA:							
Muscle mass (Kg)	44.21 ± 1.27	43.39 ± 0.95	*0.246*	41.60 ± 1.03	41.04 ± 0.89	*0.072*	*0.130*
Fat mass (Kg)	31.97 ± 2.76	27.19 ± 2.14	< 0.001	28.65 ± 1.99	26.30 ± 2.30	0.018	*0.352*
Bone mass (Kg)	2.34 ± 0.07	2.33 ± 0.06	*0.812*	3.62 ± 1.37	2.18 ± 0.05	0.016	*0.324*
Water (Kg)	33.13 ± 1.08	32.47 ± 0.98	*0.155*	31.45 ± 1.18	29.72 ± 0.98	0.026	*0.303*
Basal metabolism (Kcal)	1411.00 ± 31.15	1394.00 ± 42.81	*0.110*	1330.00 ± 34.42	1315.00 ± 31.96	*0.092*	0.092
Waist circumference (cm)	101.10 ± 3.74	95.07 ± 3.35	< 0.001	100.80 ± 3.19	95.35 ± 3.25	0.002	*0.953*
Hips circumference (cm)	111.00 ± 2.99	104.70 ± 2.77	< 0.001	110.60 ± 2.60	107.10 ± 2.90	0.012	*0.922*
Waist Hips Ratio (WHR)	0.91 ± 0.02	0.91 ± 0.02	*0.454*	0.91 ± 0.02	0.88 ± 0.02	*0.056*	*1.000*
SYS (mmHg)	131.30 ± 4.24	120.00 ± 3.42	0.002	124.60 ± 2.97	127.30 ± 3.52	*0.289*	*0.220*
DIA (mmHg)	80.00 ± 1.76	74.33 ± 2.00	0.027	77.31 ± 1.76	74.62 ± 2.50	*0.297*	*0.292*

BMI: Body Mass Index, BIA: Body impedance analysis, SYS: Systolic arterial pressure, DIA: Diastolic arterial pressure.

Data are expressed as mean ± SEM. [a]p-value derived from Wilcoxon matched-pairs signed rank test T1 *vs* T0. [b]p-value derived from Mann-Whitney test T0 group A *vs* T0 group B.

In group A, the lower weight, BMI, and fat mass, were significantly correlated with increased V scores in the SF-36 questionnaire (rho=-0.527, p = 0.038; rho=-0.546, p = 0.045; rho=-0.510, p = 0.033, respectively). Moreover, statistically significant correlations between weight loss, reduction of hips circumference, and the RP score (used to assess role limitations due to physical health; rho=-0.610, p = 0.009 and rho=-0.576, p = 0.013, respectively) were found. In group B, after 3 months of the control balanced diet, a significant decrease in bone mass and water content have been measured (Table 1).

The improvement in the HAQ score, observed in both groups, can be traced back to the moderate calorie restriction to which all patients were subjected, that produced weight reduction significantly correlated with HAQ in group B (rho = 0.586, p = 0.044).

3.7. Laboratory parameters

The metabolic, hematological and biochemical parameters analyzed are reported in Table 2. Patients did not differ significantly at T0 (see last column).

Table 2
Laboratory data of recruited patients in groups A and B.

	group A (n = 15)		p-value[a]	group B (n = 13)		p-value[a]	p-value[b]
	T0	T1		T0	T1		
OGTT:							
Basal (mg/dL)	94.21 ± 3.78	84.33 ± 2.28	< 0.001	90.00 ± 2.06	85.46 ± 2.24	0.001	0.358
After 120 min (mg/dL)	134.36 ± 9.41		-	129.31 ± 7.53		-	0.685
Insulin (μUL/mL)	12.79 ± 2.24	8.64 ± 0.93	0.058	8.89 ± 1.17	8.48 ± 0.96	0.635	0.152
HOMA index	3.07 ± 0.56	1.82 ± 0.21	0.018	1.97 ± 0.25	1.79 ± 0.20	0.385	0.101
Total Cholesterol (mg/dL)	201.90 ± 8.19	196.50 ± 5.90	0.454	206.10 ± 8.99	211.30 ± 9.89	0.480	0.732
HDL-Cholesterol (mg/dL)	61.00 ± 4.37	62.33 ± 4.68	0.877	61.00 ± 3.37	61.69 ± 3.50	0.373	1.000
Triglycerides (mg/dL)	165.10 ± 37.10	126.60 ± 21.78	0.066	116.80 ± 13.39	102.80 ± 12.21	0.157	0.259
Leukocytes (n x 10^3/μL)	8.18 ± 0.72	6.76 ± 0.47	0.003	7.02 ± 0.47	6.21 ± 0.40	0.110	0.204
Neutrophils (n x 10^3/μL)	4.70 ± 0.63	3.71 ± 0.45	0.007	4.10 ± 0.43	3.33 ± 0.21	0.146	0.453
Lymphocytes (n x 10^3/μL)	2.58 ± 0.17	2.43 ± 0.16	0.095	2.56 ± 0.21	2.35 ± 0.22	0.251	0.941
Hemoglobin (g/dL)	13.07 ± 0.17	13.17 ± 0.14	0.158	13.59 ± 0.20	13.32 ± 0.26	0.258	0.057
Platelets (n x 10^3/μL)	270.20 ± 13.77	267.50 ± 14.17	0.429	282.20 ± 17.30	268.10 ± 18.84	0.197	0.588
ESR (mm/h)	21.53 ± 3.74	21.27 ± 3.47	0.729	15.92 ± 3.43	22.24 ± 4.63	0.071	0.285

OGTT: Oral Glucose Tolerance Test, HOMA index: Homeostasis Model Assessment, HDL: High density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive Protein, GOT: Glutamic-Ossalacetic Transaminase, GPT: Glutamic-Pyruvic Transaminase.

Data are expressed as mean ± SEM. [a]p-value derived from Wilcoxon matched-pairs signed rank test T1 vs T0. [b]p-value derived from Mann-Whitney test T0 group A vs T0 group B.

	group A (n = 15)		p-value[a]	group B (n = 13)		p-value[a]	p-value[b]
	T0	T1		T0	T1		
Total Proteins (g/dL)	7.47 ± 0.14	7.23 ± 0.11	0.115	7.30 ± 0.11	7.34 ± 0.11	0.555	0.359
hs-CRP (mg/L)	0.65 ± 0.12	0.46 ± 0.06	0.039	0.60 ± 0.13	0.44 ± 0.05	0.297	0.780
Albumin (g/dL)	4.18 ± 0.09	4.24 ± 0.09	0.296	4.09 ± 0.08	4.12 ± 0.07	0.569	0.468
Transferrin (mg/dL)	289.40 ± 10.61	271.60 ± 8.18	0.013	292.30 ± 8.62	284.20 ± 11.32	0.134	0.837
GOT (U/L)	32.73 ± 3.56	27.53 ± 2.15	0.237	27.15 ± 4.03	26.54 ± 3.14	0.898	0.307
GPT (U/L)	39.57 ± 5.98	36.07 ± 3.50	0.915	30.15 ± 3.67	28.23 ± 1.92	0.748	0.207

OGTT: Oral Glucose Tolerance Test, HOMA index: Homeostasis Model Assessment, HDL: High density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive Protein, GOT: Glutamic-Ossalacetic Transaminase, GPT: Glutamic-Pyruvic Transaminase.

Data are expressed as mean ± SEM. [a]p-value derived from Wilcoxon matched-pairs signed rank test T1 *vs* T0. [b]p-value derived from Mann-Whitney test T0 group A *vs* T0 group B.

Basal glucose levels in patients, after 3 months of either dietary regimen, showed a statistically significant decrease (Table 2). Deprived diet was also effective in reducing significantly the HOMA index[32] in group A. No significant changes in fasting insulin levels, blood lipid profile, total proteins and albumin were recorded (Table 2).

The number of circulating leukocytes and neutrophils, and the level of hs-CRP were also significantly decreased in group A, together with a significant reduction of transferrin (p = 0.013). The decline in leukocyte numbers was inversely correlated with an increase of the physical pain score (PP) item in the SF-36 test (rho=-0.579, p = 0.026).

3.8. Adipokines and cytokines measurements

Circulating levels of leptin were significantly decreased after 3 months of diet in both groups A and B, whereas adiponectin was unaffected. The reduction of leptin caused a significant increase of the adiponectin/leptin ratio, in both groups A (Fig. 6) and B (Fig. 7). Serum levels of the three cytokines measured (TNFα, IL-10 and INFγ) were not significantly different before and after either diet.

4. Discussion

Our study comprised RA patients with long standing, well controlled condition, under stable pharmacological treatment, and observed them during a diet with the exclusion of three food items (meat, gluten and lactose) which have been suspected of aggravating the symptoms and worsen the disease course, in comparison with a control balanced diet including those foods. The results demonstrate that the exclusion diet helps manage the physical disability, modulating disease activity and reducing arthritic pain. Moreover, the metabolic and inflammatory profiles of patients following the exclusion diet improved to a greater extent than patients on the control diet, and this might impact on the long-term cardiovascular risk of RA[33, 34].

Diet appears to be one important environmental trigger of RA, considering that an increase in the occurrence of autoimmune diseases has been documented in developed countries, in which dramatic changes in diet have taken place, with a reduction of fiber intake, and an increased consumption of animal protein and fats[3, 35, 36]. Our goal was to establish if the dietary patterns proposed in this study, in addition to drug therapy, could help to ameliorate RA activity and alleviate RA symptoms, including fatigue, pain, emotional state and mental health.

We hypothesized that the balanced and/or deprived diet may be influencing RA in several aspects, through a range of mechanisms, among them decreasing inflammation, and modifying glucidic homeostasis (HOMA index), lowering BMI, maintaining BIA parameters and anthropometric measures, modulating immunity, mental and physical health.

In fact, in our RA patients, 3 months of exclusion diet was able to significantly reduce total leukocytes and neutrophils number, being also effective in lowering CRP and transferrin levels. The same trend was detected in patients from group B, without reaching statistical significance.

In our patients, both diets were able to reduce circulating leptin levels, an adipokine with a key role also in the inflammatory response, stimulating T helper in synthetizing pro-inflammatory cytokines.

Several dietary intervention studies in RA patients have been published in the past [37–42], among them, a strict 3-month Mediterranean-based diet in RA patients ensued clinical benefits, with a significant reduction of DAS28 and improved quality of life assessed by HAQ and SF-36 compared to RA control patients on standard diets[43]. To date, there is limited but univocal evidence to suggest that the Mediterranean diet is beneficial in the prevention and treatment of pathological conditions, including RA[5, 15]. The protective effect of the Mediterranean diet on RA disease activity may be due to changes in the gut microbiota of the patients as shown in the study Prevention with Mediterranean Diet-(PREDIMED): in that study, patients following the Mediterranean diet had a significantly lower CRP values and disease activity score[44]. Others have observed that the Mediterranean diet represents a whole dietary pattern, and it may be seen as an adjuvant therapy, acting through modulating intestinal microbiota and intestinal barrier function, resulting in overall improvement of RA course[45]. Among rheumatic patients who switched from an omnivorous to a vegetarian diet, an attenuation of disease activity has been reported[41].

Defining standardized criteria for disease monitoring was one of the goals of the present clinical study. Besides objective physical articular examination, quantitative evaluations were obtained through clinimetric index and laboratory parameters CRP, ESR, blood count test, transferrin, together with lipid profile and HOMA index[46], in order to have an indication of the disease activity status (potentially reversible and indices of response to therapy) and permanent joint damage measures. Participating patients did not show significant differences at the recruitment time, also considering the different pharmacological treatment received. The general state of physical and mental health was assessed by means of the VAS score, and the SF-36 questionnaire. They both indicated improvements after the study period, which were more pronounced in group A, receiving the exclusion diet. Quality of life, tested with the HAQ questionnaire, also showed improvement, thus confirming that both dietary manipulations had a positive impact on RA patients.

Some dietary components may affect chronic inflammatory diseases, although a large prospective study of 56,075 Danish middle-aged men and women, failed to detect a higher risk of any inflammatory disease or RA specifically, for low fiber or/and high meat intake[47].

Two prospective studies investigating the intake of red meat and the risk of RA development reached opposite conclusions. A Swedish study of 35,600 women found no association[48] whereas, the EPIC-Norfolk study showed that higher consumption of red meat carried an increased risk of inflammatory polyarthritis (OR 2.3, 95% CI 1.1–4.9)[49]. These studies do not address the clinical effects of a diet rich in, or deprived of, red meat as well as other dietary components[50, 51].

Obesity in RA has been found to be associated with higher DAS28, tender joint counts, inflammatory marker levels, patient global evaluation and pain scores, as well as physical function scores. However, it was not associated with increased mortality[52]. Leptin levels, which are raised in obese, are markedly increased in RA, and related to the general inflammatory status and the disease activity[53]. In our study, both diets resulted in significant lowering of leptin, and increase of the adiponectin/leptin ratio, and more so for the exclusion diet.

Diet has a central role in increasing inflammatory disease risk and progression. Several nutrients may have protective activity for RA symptoms, whereas others may have a harmful role. Our study provides evidence that the combination of three food items removal from the diet has a positive impact on several parameters in RA patients. Gut microbiota changes and body composition modifications are probable mechanisms of how diet affects disease course and patients' perception[54].

Although attenuating effects on RA pathology were observed in our and others dietary intervention studies, none of them has been successfully implemented in the clinics so far. Maybe the reasons are due to the poorly characterized immunological mechanisms underlying the improvement in RA patients, or the availability of ever more effective drugs that make dietary alternatives less appealing. Moreover, all dietary interventions require changes to the patients' daily lifestyle and eating behaviors, and that requires commitment, endurance, persuasion, and time. For such reasons, also in our study, we registered a low level of compliance in carrying out the study for 3 months.

5. Conclusions

The results obtained appear to confirm that exclusion of common food items improves several parameters of RA patients and may have substantial health benefits. The aim of preventing complications of RA can be better achieved by including diet in the therapeutic plan. We agree with Forsyth[40] on the importance, in the dietary change, of the duration of the intervention; according to our study, 3 months represent an adequate length to detect significant changes.

Abbreviations

RA: Rheumatoid arthritis; TMAO: Trimethylamine N-oxide; c-, b-DMARDs: conventional-, biological-Disease modifying anti-rheumatic drugs; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; DAS 28: Disease Activity Score of 28 joints; VAS: Visual Analogue Scale; SF-36: Short Form Health survey; HAQ: Health Assessment Questionnaire; OGTT: Oral Glucose Tolerance Test; HOMA: Homeostasis Model Assessment index; ESR: Erythrocyte Sedimentation Rate; hs-CRP: high sensivity-C-Reactive Protein; BMI: body mass index; BIA: Bioimpedance Analysis; SYS: systolic arterial pressure; DIA: diastolic arterial pressure.

Declarations

Ethics approval and consent to participate:

All participants signed written informed consent for participation in the study. The study has been approved by the Ethics Committee of the Provinces of Chieti and Pescara and of the "G. d'Annunzio" University of Chieti-Pescara (Ethics Committee Project No.10/20).

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

RP, EC and GMT conceptualization; DC, EC, GMT study and diets design; EC, ES, DC, MB collected data and visited the patients; CDA, DC, GMT, RP analyzed the results; GMT, SL, FC, RP supervised all phases of the study; CDA wrote the first draft of the manuscript; all Authors contributed to the interpretation of results, read and approved the final version.

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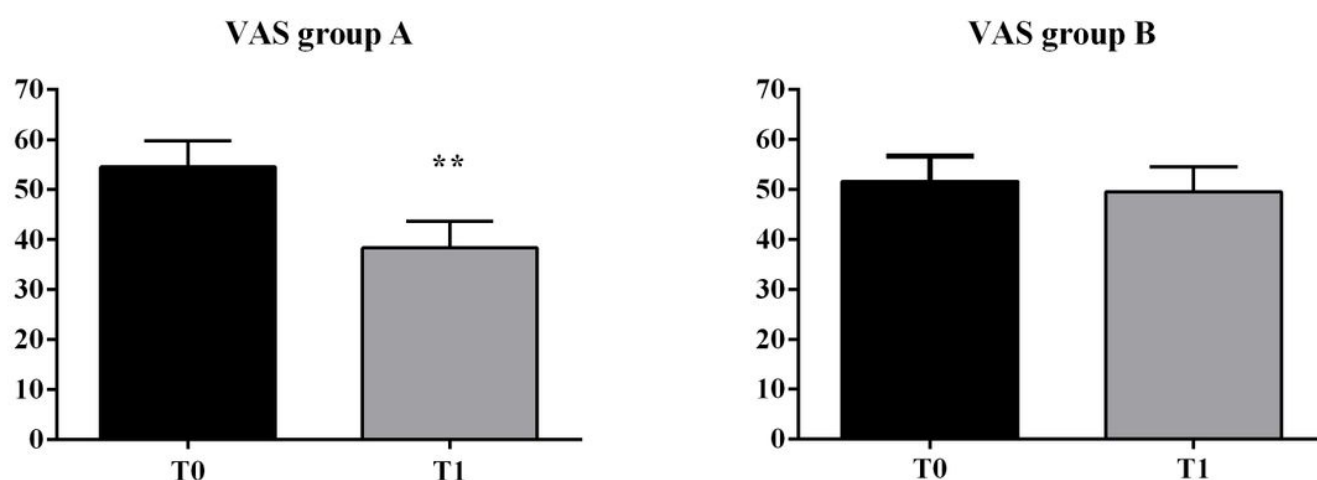
Figures

Figure 1

VAS score referred to different dietary regimens. Bar plots represent the mean±SEM of VAS scores in groups A and B. p-value derived from Wilcoxon matched-pairs signed rank test; **p<0.003 T1 VAS vs T0 VAS.
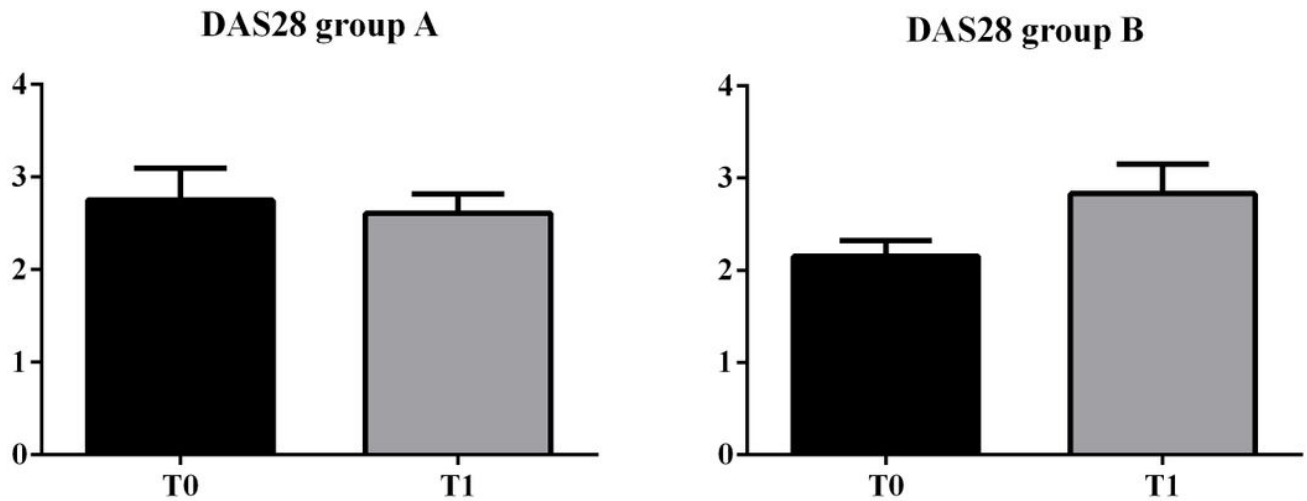

Figure 2

DAS 28 scores referred to different dietary regimens. Bar plots represent the mean±SEM of DAS 28 index in the two groups (A and B diets).
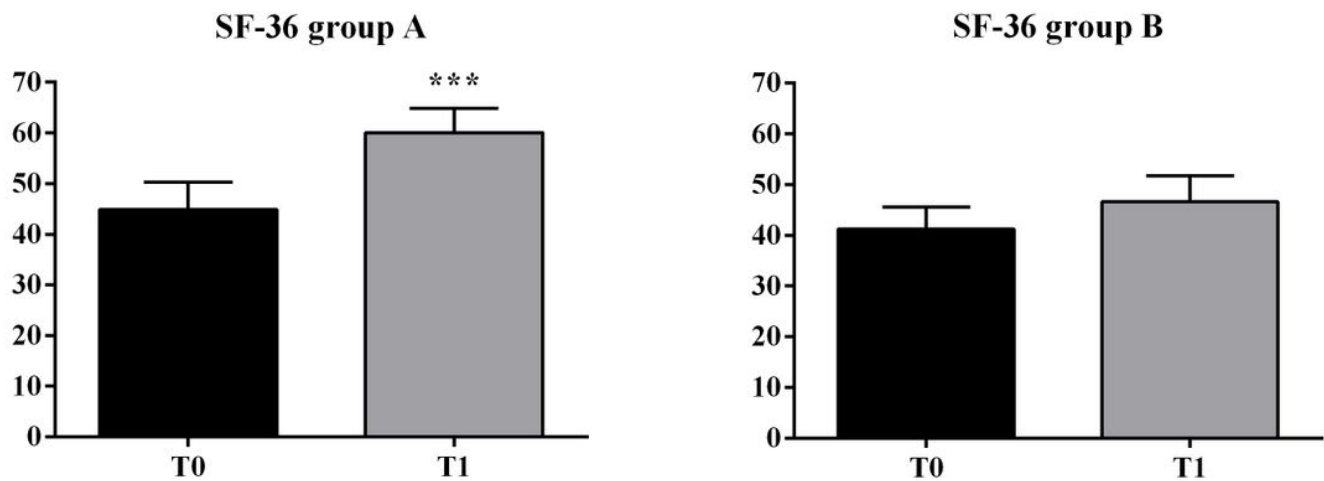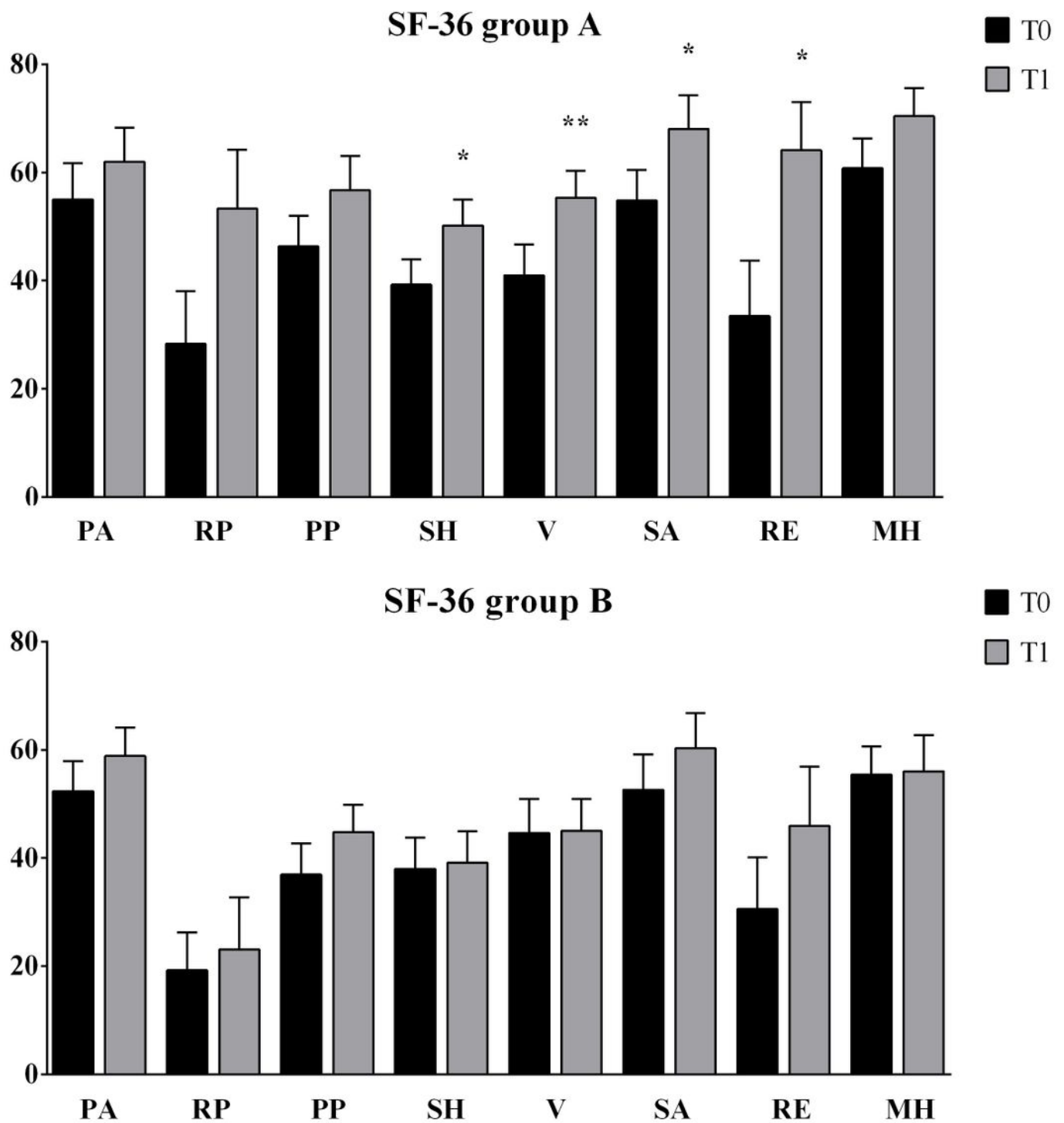

Figure 3

Total SF-36 score referred to different dietary regimens. Bar plots graphically depict the mean±SEM of SF-36 total score in groups A and B. p-value derived from Wilcoxon matched-pairs signed rank test; ***p<0.001 T1 SF-36 vs T0 SF-36.

Figure 4

Scores of the 8 items from SF-36 in group A and B. Items legend: PA, physical activity; RP, role limitations due to physical health; PP, physical pain; SH, state of health; V, vitality; SA, social activities; RE, role limitations due to the emotional state; MH, mental health. Bar plots graphically show the mean±SEM. p-value derived from Wilcoxon matched-pairs signed rank test; *p<0.05, **p<0.01 T1 vs T0.
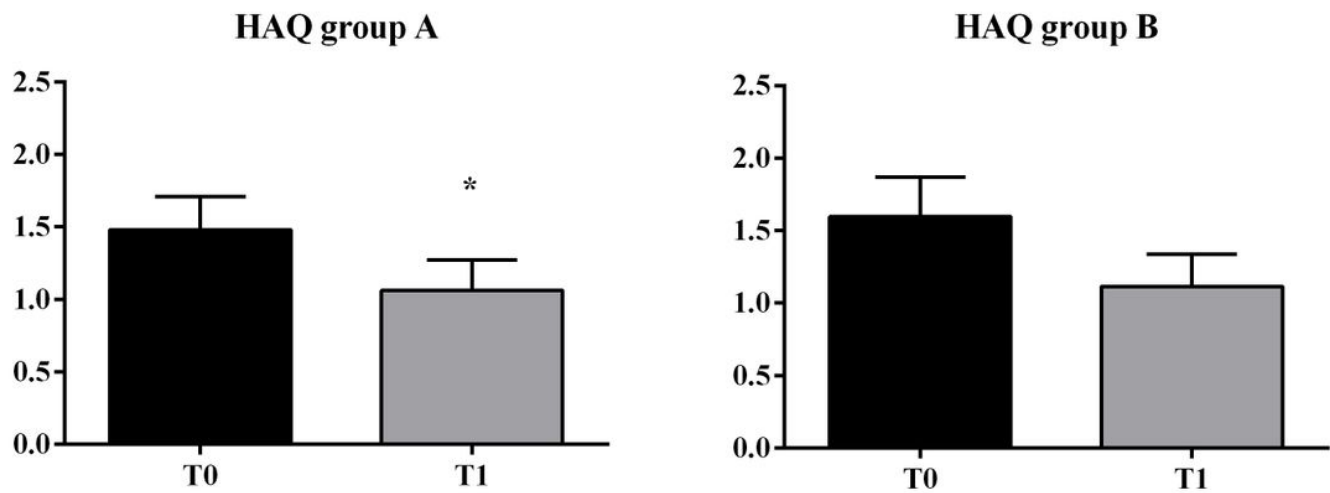
Figure 5

HAQ variation referred to different dietary regimens. Bar plots graphically depict the mean±SEM of HAQ score in groups A and B. p-value derived from Wilcoxon matched-pairs signed rank test; *p<0.05 T1 HAQ vs T0 HAQ.
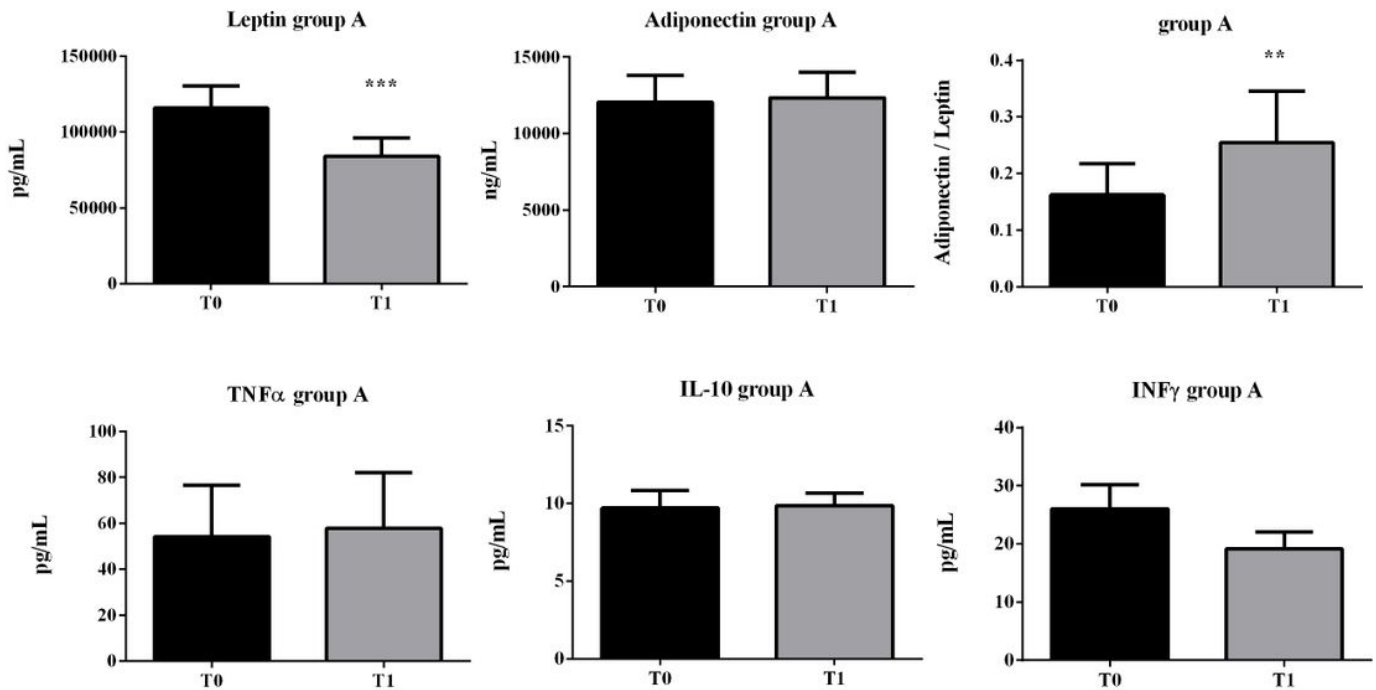

Figure 6

Bar plots represent the mean±SEM of adipokines and cytokines measured in sera of patients belonging to group A. p-values derived from Wilcoxon matched-pairs signed rank test; **p<0.01, ***p<0.001, T1 vs T0.
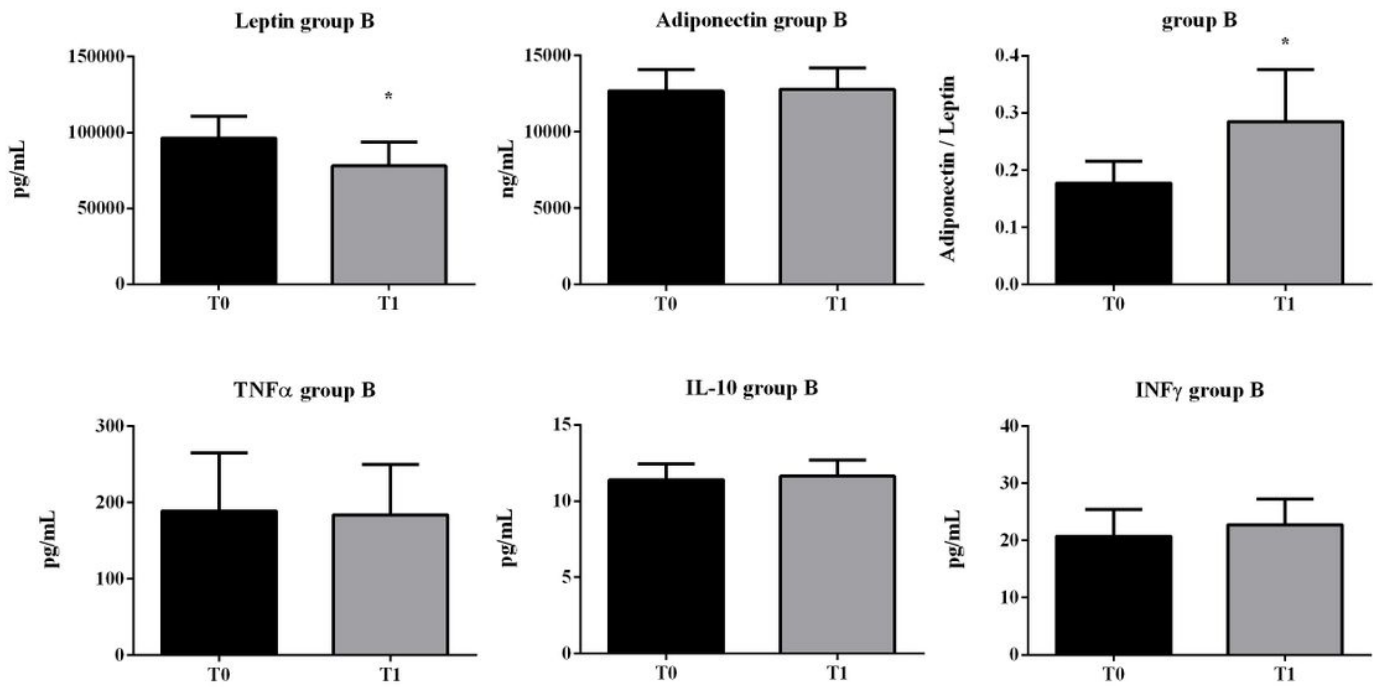
Figure 7

Bar plots represent the mean±SEM of adipokines and cytokines measured in sera of patients belonging to group B. p-values derived from Wilcoxon matched-pairs signed rank test; *p<0.05, T1 vs T0.