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Review

Weight loss is a critical factor to reduce inflammation

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SUMMARY

Background: Chronic inflammation is a process sustained by the augmentation of circulating cytokines level and C-reactive protein (CRP). Adipocytes and adipose tissue infiltration with inflammatory cells, are an important source of adipokines production, and their expansion due to overnutrition is responsible for increased in inflammation. The reduction of body fat following both controlled diets or gastric surgery can be favorable in the reduction of pro-inflammatory cytokines.

Methods: A systematic literature search performed using PubMed, Google Scholar and Cochrane Library database screened for clinical and randomized controlled trials (RCTs) using the combination of the following keywords: "weight loss, inflammation," "restricted diet, anti-inflammatory effect." Studies including diet intervention, weight loss after gastric surgery have been included. Multidisciplinary program with the addition of food supplements, exercise, or drugs have been excluded to avoid their interference with the regulation inflammatory markers.

Results: Out of 967 articles found, 76 were selected, including a total of 6742 patients with a mean age of 44.0 ± 3,3 years and a BMI of 33 ± 6.6. The observation period ranged from 3 weeks up to two years with an average weight loss per month of 1.1 kg. In most of the studies, it was found that weight loss caused a significant reduction of plasma level of inflammatory cytokines although three studies did not see any effect.

Conclusions: In obese and overweight subjects weight loss, induced both by energy-restricted diet or surgery, is a determinant factor for reducing the level of pro-inflammatory markers. Hypocaloric diet has an anti-inflammatory effect independent of the diet composition which can play an important role in the prevention of chronic diseases.

1. Introduction

Chronic inflammation represents the primary source of metabolic disorders promoting the onset of insulin resistance [1,2], atherosclerosis [3], neurodegenerative and cardiovascular disease (CVD) [4], obesity and cancer [5,6]. Markers of inflammation, although there is no consensus about which tag represents various degree of inflammation, include: leucocytes, granulocytes, fibrinogen, CRP, serum amyloid A, CPR and the adipokinesTNF-α, IL-6, IL1b, IL-8, leptin, adiponectin, resistine plasminogen activator inhibitor-1 (PAI-1) [7,8]. CRP is a protein secreted by hepatocytes in response to systemic inflammation and represents the most frequently used test to detect inflammatory state [9]. High-sensitivity CRP (hs-CRP) is more specific and correlated with obesity [10] and predict the major cardiovascular events [11] and heart failure [12]. Pro-inflammatory cytokines are produced by body fat [13] so that body fat accumulation represents an essential source of adipokines and inflammatory responses [8] contributing to the development of metabolic disorders [14] and CVD [15].

Insulin resistance, is activated by cytokines signaling at the level of various target tissues, primarily in body fat cells, but also at liver and skeletal muscle level [16] and represents a critical factor worsening the metabolic conditions and promoting the development of type-2 diabetes, cardiovascular disease [17], and neuropathy [18]. A high energy and high-fat diet is implicated in the activation of numerous pro-inflammatory biomarkers such as CRP, IL-1, IL-6, IL-8, TNF-α, and MCP1, promoting the development of many chronic diseases including cardiovascular disease [19] neurological disease and cognitive decline [20], metabolic syndrome, aging, and cancer [21]. The healthy metabolic subjects can be described as individuals with a lower level of inflammatory markers [22].

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So that, considering the inflammatory impact of diet on inflammatory cytokine secretion, the nutritional therapy could represent a vital prevention strategy on chronic diseases. This review is focused on the specific impact of weight loss on inflammation.

2. Methods

A systematic literature search was performed using PubMed, Google Scholar and Cochrane library were screened for randomized controlled trials (RCTs) clinical trials using the combination of the following keywords: "weight loss and inflammation," "restricted diet and anti-inflammatory effect." All studies enrolling patients following a weight loss program both by diet restriction diet or gastric surgery with low to severe inflammation state were considered. Follow-up performed with healthy diets and no changes in body weight were excluded. Clinical trials using the addition of food supplements, drugs, and exercise were excluded as well as retrospective study design. Studies considering healthy obese subjects, type-2 diabetes, metabolic syndrome (MetS) were included.

3. Results

Out of 967 retrieved articles, 76 were selected, including a total of 6.742 patients with a mean age of 44.0 ± 33.2 years and are reported in the flowchart in Fig. 1. The studies have been classified into in three groups: weight loss by diet intervention (Table 1), weight loss by bariatric surgery (Table 2) and effect of weight loss on gene expression (Table 3).

Table 1 summarizes the clinical studies which evaluated the effect of different types of diets ranging from very low-calorie diet (VLCD), low calorie diets (LCD), Mediterranean diets on serum inflammatory markers. Between the studies, considerable differences in the number of patients, duration of diet treatment, variety of nutritional programs prescribed and cytokines detection assays exists. The studies have been divided in two groups: one including a large number and another a small number of patients to evidence possible statistics differences. The large number of patients studies were conducted on a population including a mean number of subject of 378 ± 263, with a mean age 48.4 ± 11,14 and a weight loss of 7.3 ± kg in a mean time of 11.6 ± 6,6 months found a significant reduction of inflammatory markers [23–36] except Van Bussel et al. [35], the most prolonged study reported lasting seven years in patients following an healthy diet, but without significant weight loss, showed an improvement in endothelial function, but no changes in inflammatory markers.

The smaller groups of patients included a mean number 49 ± 24,2, with a mean age of 46,7 ± 10,7, and mean weight loss of 7,78 ± 3,8 Kg of during 6,7 month of diet therapy [29,32,37–76]. In the smaller groups of patients the body weight loss is more accentuated.

The duration time of diet varyed from a minimum of two weeks [49] until three years [76], a few studies one year [23,44,47,55,77,78] and the majority 2 months [39,48,57,69,74,76,79–81]. The diet program also had a wide range of variability. Some authors adopted the Mediterranean diet style [38,69,81], other the very low calories diet (VLCD) of about 600–800 Kcal/day [32,52,76,82–84]. The VLCD followed by the patients were not ketogenic because the formation of ketone bodies is associated with a high fat intake in absence of dietary carbohydrates [85]. In the studies a significant disparity in the

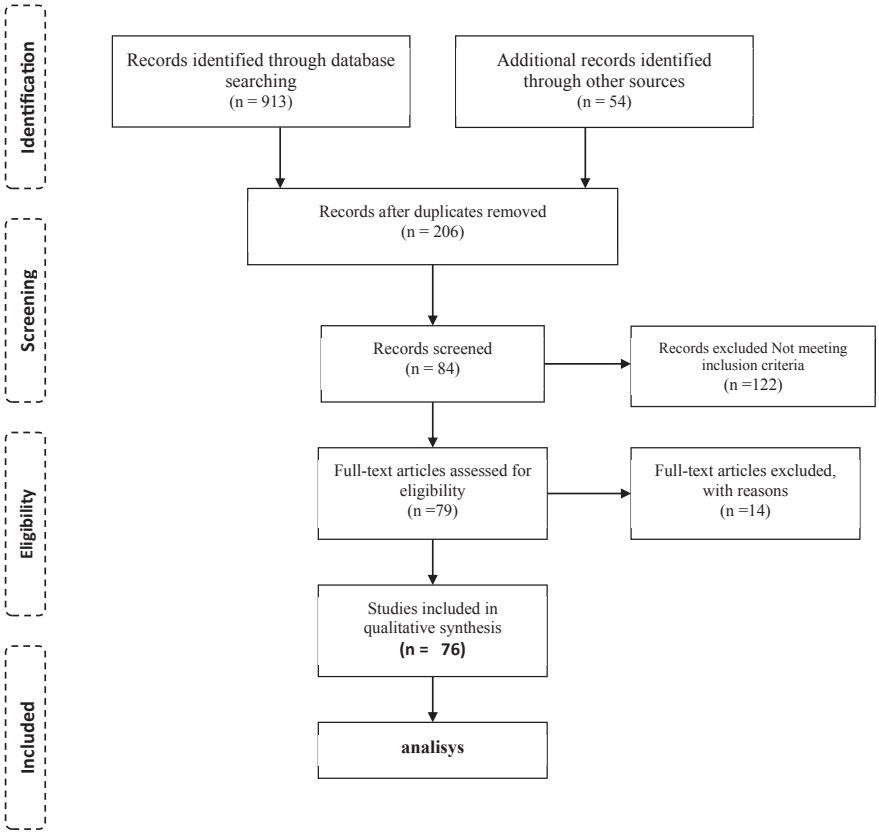

Fig. 1. Flow chart showing the methodology of selection of the articles.

Table 1
Effect of weight loss on inflammatory markers.

Authors	Subjects	Age	BMI	Study design	Diet type	Time (months)	Weight loss Kg	CPR	IL-6	TNF-α	Comment
Merra, 2017 [37]	54	44.6	31.3	randomized double-blind trial with placebo	VLCD VLCKD 500 Kcal	0.75	4.5	↓	ND	ND	Reduction in CRP, NF-κB, SOD1 and chemokines
Dyer, 2017 [38]	38F 11M	60	32	Randomized clinical trial	Mediterranean diet style FFQ	4	1.5	—	NC	NC	No changes in inflammatory markers. Only reduction in IL-1α
Möller, K. 2016 [39]	42 M, W	49.9	32.7	Randomized clinical trial	Formula diet 1285.7/1789.5 Kcal	2	7.19 6.78	↓	↓	↓	Moderate weight loss determined a significant improvement in the inflammatory state
Kirwan, 2016 [40]	27 W 6 M	39	33.1	Randomized Controlled Trial	1.Whole-grain 2.refined-grain diet Kcal 2168	2 Washout 2	1.2.4 1.2.5	NC	ND	ND	Reduced IR and increased adiponectin level. CRP unchanged
Rock, 2015 [23]	245 W obese	50	33.5	Follow up	Lower fat diet lower CHO diet 500/1000 kcal less basal EE	12	9.2 6.5	↓	↓		Weight loss, rather than diet composition, is the most critical factor for reducing chronic inflammation
Meydani, 2016 [24]	218 99F/44M	38	25.1	randomized clinical trial	25% calorie restriction	24	15.9	↓	↓	↓	Reduction in total WBC, ICAM-1, leptin, RP and TNF-α of about 40 −50%
Pedersen, 2016 [41]	70 (57M + 13W) CAD	63.3	31.1	Randomized Controlled Trial	Aerobic exercise LCD 800-100 Kcal/die	3	1.5 9	↓	↓	↓	LCD diet decreased inflammatory markers whiel exercise did not.
Magkos, 2016 [42]	40 (19 weight loss 16W + 3M)	46 43	37.9	Randomized Controlled Trial	20 Weight maintenance 20 weight loss	6 3.5 6.8 10.4	— 5.9 11.3 16.8	↓	NC	NC	11%−16% weight loss reduced IR, leptin and CRP. Adiponectin, MCP- 1 and IL-6 unchanged.
Song, 2016 [43]	92 47 M 45 W	36.4	26	randomized, controlled	Eucal = 2661 Kcal LCD = 1881	1,5	1 5	↓ ↓	—	—	Low fat diet reduces adiponectin. Varying macronutrients no different effect on inflammation markers
Ho, 2015 [44]	15 W 13 M	39	33.2	Randomized clinical trial		12	9.4	↓	↓	—	Significant decrease in leptin, resistine, IR, and PAI-1.
Hu, 2015 [25]	148 healthy	45.8 47.8	35 36	Randomized Controlled Trial	low-CHO diet low fat diet	12	5.3 1.3	ND	↓	↓	The two diets had equivalent effects on other citokynes.
Ryan, 2015 [45]	71 W	60	29	Prospective controlled study	1. Isocaloric 2.Isocaloric + exercise	6	8%	↓	ND	ND	Plasma sICAM-1, CRP, IR reduce more in exercise group
Khoo, 2015 [46]	80 M	42.6	32	Randomized Controlled Trial	Reduced intake Kcal 500 Exercise 200−300 min/week	6	2.7 3.9	↓	ND	ND	Exercise group showed greater fat reduction and inflammatory markers
Beavers, 2015 [26]	450 Obese osteoarthritis	65.6	33.6	randomized controlled trial	Diet + exercise Diet only Exercise only	18	3.5 (?)	↓	↓	—	Reduction of 5% total weight and fat decrease in all measures of body fat mass
Miller, 2014 [47]	30 15 usual care 15 life style	58	34	Randomized Controlled Trial	1200−1800 kcal	12	7.8% 4.5	↓	↓	↓	Weight loss improves all inflammatory markers level, leptin, adiponectin, CRP, IL-6, TNF-α, and PAI-1.
Jonasson, 2014 [220]	27 M 32 W	63	34 32	Randomized Controlled Trial	LFD = 1809 with LCD = 1690	6	4.0 4.3	ns	↓	—	LCD improve inflammatory state in T2D
Juanola-Falgarona, 2014 [36]	122	43.5	31	Randomized Controlled Trial	- moderate-CHO high-GI - moderate-CHO low-GI - low-fat and high-GI diet	6		↓	↓	↓	LCD with moderate CHO is more effective in reducing body weight and insulin resistance.

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Table 1 (*continued*)

Authors	Subjects	Age	BMI	Study design	Diet type	Time (months)	Weight loss Kg	CPR	IL-6	TNF-α	Comment
Lopez-Legarrea, 2014 [48]	96 (48% W)	50	35.8	Randomized controlled trial	Protein gr. 78.2 Fats gr. 56.6 CHO gr. 114.6	2	7	↓	↓	↓	CPR, IL-6, TNF-α and PAI-1 significantly correlated with high protein intake
Strasser, 2015 [49]	16 W 22 M	52.8	29	Randomized Controlled Trial	VLCD; O 600 kcal/day LCD 1200 kcal/day	0.5	3	ND	ND	ND	No changes in inflammatory markers neopterin, and tyrosine. Leptin reduced.
Richard, 2013 [219]	26 M MetS	49.4	ND	Controlled Clinical Trial	Isocal Am diet Isocal Med die 500 kcal reduc	5 weeks 5 weeks 10 weeks	0 0 5%	↓	↓	↓	MedDiet even in the absence of weight loss significantly reduces inflammation.
Trussardi Fayh, 2013 [50]	48	31.8	34.8	Randomized Controlled Trial	Diet (2090 kcal) Diet + exercise	2,5 (79 days)	4.3	↓	ND	ND	Exercise did not add effect of weight loss induced by diet on the reduction of IR and CRP.
Nicklas, 2013 [29]	710 435 W 275 M	52	NR	Randomized Controlled Trial	fat, protein, CHO 20, 15, 65%; 20, 25, 55%; 40, 15, 45%; 40, 25, 35%, respectively[a]	24	6.7 1st year 5.4	↓	—	—	Weight loss decrease CRP independently of dietary composition.
Blesso, 2103 [51]	12 M 25 W	51.9	30.5	Randomized Controlled Trial	moderate carbohydrate-restricted diet (<30% energy)	3	3.6	NC	↓	NC	Reductions in TNFα and serum amyloid A. Other markerker unchanged
Tajik, 2013 [52]	29 obese W	37.5	30	Clinical Trial	Restriction of caloric intake of 500–1000	3	10%	nd	↓		Reduction in IL-6 and IL-18 in obese women.
Stendell-Hollis, 2013 [30]	129 W breastfeeding	29.7	27.2	Randomized Controlled Trial	1.Mediet (2711 Kcal) 2.comparison diet	4	2.3 3.2	Not tested	NC	↓	Decrease in TNF-α, not IL-6 was in both diet groups
Hegen, 2012 [31]	181 M &W	30–65	28–40	Randomized Controlled Trial	2 Hypocaloric diet: a low-fat or low-glycemic-load diet	3	4.4	↓	↓	↓	Hypocaloric diets reduced also leptin and PAI-1 independent of dietary composition.
Gogebakan, 2011 [32]	932	41	34	Randomized Controlled Trial	low-calorie diet (800 kcal) ad libitum diets	6.2	11.2	↓	ND	ND	Low-glycemic index and low protein diets achieved the greater reduction in CRP
Neuhouser, 2012 [53]	40 normal 42 obese	29.5 32.5	22.4 32.5	Randomized Controlled Trial	Identical macronutrients. High-glycemic load diet Low glycemic load diet	n.s.	n.s.	↑ ↓	—	—	Low glycemic load determine a reduction in inflammation
Imayama, 2012 [33]	439 W	58.1	31	Randomized Controlled Trial	1.hypocal diet 2.exercise 3.diet + exercise	12	6.6 5.6 7.5	↓	↓	ND	Weight loss diet with or without exercise reduces biomarkers CRP, SAA, and IL-6.
Golan, 2012 [34]	322 277 M 45 W	52	31	Randomized Controlled Trial	1.low fat diet 2.Med diet 3.low carbo diet	24	T2D 3,4 4.1	↓	___	___	CRP in subjects without diabetes
Khoo, 2011 [46]	31 M T2D	59.7	>30	Randomized Controlled Trial	1000 kcal/day 600 kcal/day (low-fat, high-protein)	2	10% 5%	↓	↓	ND	CRP and IL-6 decreased with the high protein diet.
Johnstone, 2011 [68]	16 M obese	55	>35	randomized clinical trial	two high-protein diets (30% of energy), a) low CHO (4% carbohydrate, b) moderate CHO 35%	1	6.7 4.3	ND	↓	↓	IR, lipaemia and inflammation improved similarly on both diets.
Hermsdorff, 2011 [82]	24F 17M	37	32.2	Controlled Clinical Trial	caloric-restricted diet	2	4.4	↓	↓	↓	Reductions on proinflammatory markers CRP and C3.
Fisher, 2011 [27]	126 W	24–41	28	Randomized Controlled Trial	1.Diet (800 kcal) 2.Diet + aerobic 3.Diet + resistance training	1 month	12	↓	↓	↓	weight loss has a more profound anti-inflammatory impact while exercise did not.
Gögebakan, 2011 [32]	932	41	34	multinational cohort study		2 4.2	11,2 —	—	↓	—	Low-glycemic-index diets and lesser protein content reduced CRP

					800 kcal/day Mintanance diet (different CHO and protein %)					
Christiansen, 2010 [70]	(W = 59) (M = 29)	37.2 35.6 37.5	33.335.3 34.2	Randomized Controlled Trial	1.Exercise 2.diet 3.diet + exercise	3	3.5 12.3 12.3	___	___	___	In diet group MCP-1, MIP-1alpha, IL-15, and IL-18 decreased, adiponectin increased
Davis, 2011 [71]	51 obese T2D	55	35.5	Randomized Controlled Trial	1642 Kcal 1810 Kcal low-CHO (33.4% CHO) low-fat diet (30.8% fat).	6	11.1	↓	↓	—	Both low-CHO and low-fat diets reduced inflammatory markers level
Bladbjerg, 2011 [72]	22 M 32 W	29.2 27.2	31	Randomized Controlled Trial	1.high MUFA 2. low fat 3.controls 2390 Kcal	6	NC	↓	ND	___	No significant differences in changes induced by the different diets.
Sola, 2009 [73]	67 42 W 25 M	34	46	Case-Control Studies	1 month VLCD 2 months low calories 1200/1500 kcal	1 2	10.9	NC	NC	NC	No improvement in inflammatory markers.
Hermsdorff, 2009 [69]	24 F 17 M	37	32	Controlled Clinical Trial	hypocaloric Mediterranean diet	2	4.4	↓	↓	↓	Hypocaloric diet resulted in specific reductions on RBP4, IL-6, TNFα.
Campion, 2009 [74]	12 M 12 W	34	30.5	Controlled Clinical Trial	hypocaloric diet (food questionnaire) 55% as CHO, 15% as protein 30% as fat	2	7.7 5.4	ND	↓	ND	TNF-α metilation and levels positively correlated with weight loss
De Mello, 2008 [75]	10 M 14 W	58	33	Randomized Controlled Trial	reduced caloric intake of about 500 kJ/day	8.1	4.6	↓	↓	↓	Weight reduction resulted a decreased mRNA expression of IL-1beta (IL1B), TNF-α and an increase in IL-6 and IL-8
Madsen, 2008 [76]	93 obese	37.2	35	Double-Blind	800 kcal/day	2 36	7,7 14,3	↓	—	—	10% of weight loss determines an improvement in adipnectin level, CRP and fibrinogen
Salas-Salvadó, 2008 [28]	772 (339 M) (433W)	67.6 69.8	29 30.3	Cross-Sectional Studies	food frequency questionnaire for adherence to Mediterranean diet	___	___	↓	↓	ND	Mediterranean foods lowered the concentrations of inflammatory markers.
Bougoulia, 2006 [54]	36 W 30 W healthy	35.4 34.9	38.5 24	Controlled Clinical Trial	Hypocaloric diet (−600 kcal of energy expenditure)	6		↓	—	—	Improvement in IR and glutathione peroxidase activity
Kasim-karakas,, 2006 [55]	22 W Postmenopausal	61	29.1	Controlled Clinical Trial	eucaloric low- fat high CHO diet (Kcal 2238) and ad libitum (kcal 1251)	12	6 6	↓	↓	—	Low-fat, high-carbohydrate determines a decrease in serum amyloid A and an increase of adiponectin.
Clifton, 2006 [221]	55	49.3	31.8	Randomized Controlled Trial	Kcal 1434	3	6.3	↓	NC	___	CRP, PAI-1 and sICAM1 reduced. IL-6 no changes
Giannopoulou, 2005 [56]	33 W	57.4	33.7	Randomized Controlled Trial	1.diet alone (−600 Kcal) 2.exercise 3.diet + exercise	3.2	4.5	↓	↓	NC	CRP decrease in all groups. Leptin only in diets groups. Resistin, TNFα and adiponectin no changes
Jellema, A. 2004 [57]	11 obese men	59	31.3	Double-Blind Clinical Trial	Fish oil + diet Hypocaloric diet	2	9.4	↓	↓	↓	Superior effect of diet compared to fish oil addition
Nicklas, 2004 [29]	71	68	34.4	Randomized Controlled Trial	Caloric intake reduced of 500 kcal/day	18	10.6	↓	↓	____	Significant reduction of CRP and IL-6, but not TNF-α only in weight loss group.
Sharman, 2004 [58]	15 men	33.2	34.3	Clinical Trial	low-fat diet and a very-low-carbohydrate diet (kcal 1840)	1.5	6.5	↓	↓	↓	After weight loss, Improvement of CAM-1 level also.
Arvidsson, 2004 [59]	40 W	35.3	37.6	Randomized Controlled Trial	VLCD moderate-fat/ moderate-carbohydrate or low-fat/high-carbohydrate	2.5	7.7	ND	↓	↓	Reduced levels of leptin, IL-6, IL-8, TNF-α, and PAI-1. No changes in adiponectin.

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Table 1 (*continued*)

Authors	Subjects	Age	BMI	Study design	Diet type	Time (months)	Weight loss Kg	CPR	IL-6	TNF-α	Comment
Seshadri, 2004 [60]	43 W 35 M	55 54	43 44	Randomized Controlled Trial	1.Low CHO diet (2100 Kcal) 2.conventional (2122 Kcal)	6	8.5 4.9	↓			Low-carbohydrate diet had favorable effect on lipoprotein and inflammation
Xydakis, 2004 [61]	56 W 24 M	47.1	38.3	Clinical trial	VLCD 600–800 kcal	1–1.5	8.1	↓	ND	↓	Improvement in leptin and IR and TNF-α. No change in adiponectin, CRP.
You, 2004 [62]	17 W 17 M	57 59	32.7	Randomized Controlled Trial	1.Diet (250–350) deficit 2.Diet + exercise	6	7.3	↓	↓	↓	Diet plus exercise, but not diet alone reduced markers of inflammation
Bruun, 2003 [63]	19 M	18–48	38.6	Clinical trial	1000 kcal for 8 weeks followed by 1481 kcal for further 8 weeks	4	19	ND	↓	↓	Weight loss caused a decrease of IL-6 and TNF-α and increase of IL-8.
Bruun, 2002 [64]	89 50 M 39 W	20–57	34.2	cross-sectional study	VLCD of 800 kcal	2	13	ND	ND	↓	Weight loss decreased TNF-α and increased IL-8
Tchernof, 2002 [66]	25 W Healthy	56.4	35.6	Clinical Trial	1200 kcal	13.9	14.5	↓			Weight loss decreased plasma CRP levels.
Heilbronn, 2001 [67]	83 W healthy	48	33.8	Clinical Trial	1362 Kcal Fat 15%	3	7.9	↓	ND	ND	CRP lowered in proportion to weight loss.
Bastard, 2000 [65]	8 W lean 14W obese 7 W T2D	42 45 58	20 39.5 36.6	Clinical Trial	VLDC	0.75	4	↓	↓	No changes	VLCD induced a decrease in IL-6 and leptin in adipose tissue and serum.

PGF2-α = prostaglandin F2 alpha; UNCR = urinary N-acetyl glucosaminidase/cretine ratio; low-fat diet (LFD) with a low-carbohydrate diet (LCD); CHO = carbohydrates; EE = energy expenditure; VLCD = very low calory diet; VLCKD1, in which 50% of protein intake is replaced with synthetic amino acids; GI = glycemic index; RYGBP = Roux-en-Y gastric bypass; PAI-1 = plasminogen activator inhibitor 1; sICAM-1 = soluble intracellular adhesion molecule-1; PUFA = polyunsaturated fatty acids; SOD1 = superoxide dismutase; ND = not detected; NR = not reported; FFQ = food frequency questionnaire; IR = insulin resistance; SAA = serum amyloid A; RPB4 = retinol binding protein-4; M = men; W = women; T2D = type-2 diabetes.

[a] 750 kilocalories/day energy deficit from total energy requirements.

Table 2
Effect of weight loss by gastric by-pass surgery on serum inflammatory markers.

Authors	Patients	Age	BMI (kg/m^2)	Type of study	Study design	Weight loss (kg)	Duration (months)	CRP	IL-6	TNF-α	Results
Hanusch-Enserer, 2003 [93]	24 W	nn	40	Clinical trial	LAGB	20	12	↓	ND	ND	Improvement of inflammation, complement factors C3 and C4, and irregularities in leukocyte and lymphocyte
Cancello, 2005 [92]	7 lean 17 obese W	43.5	21.9 48	Longitudinal Study	RYGBP surgery	22	3	↓	ND	ND	Reduction of MCP-1 leptin, CRP, SAA, macrophages in WAT.
Dalmas, 2011 [78]	33 obese 18 ob + T2D	39.7 47.9	48.2 52.8	Comparative Study	RYGBP Kcal 1446	30	12	↓	↓	↓	Drastic weight loss reduced significantly cytokines level
Moschen, 2010 [91]	20 obese	35.5	43.5	observational	LABG	26.1	6	↓	↓	↓	Weight loss reduced IL-6 and TNF-a mRNA more pronounced in adipose tissue.
Miller, 2011 [47]	27	45.9	55.1	Longitudinal study	RYGBP	25.7	6	↓	↓	ND	Pro-inflammatory biomarkers decreased independent of the magnitude of weight loss.
Bueter, 2010 [90]	34	40,2	44,6	Controlled Clinical Trial	LAGB RYGB LSG	10	1	↓	ND	ND	Improvement of inflammatory markers and urinary cytokines.
Illán-Gómez, 2012 [89]	60 W	40.3	47.6	Cohort study	RYGBP	27 40 47	3 6 12	↓	↓	↓	Significant decrease in inflammatory markers, adiponectin increase
Lima, 2013 [77]	20 W	35.8	46.3	Randomized Controlled Trial	- RYGBP - omentectomy	9.3 12.6	12	↓	___	___	Omentectomy reduced CRP level, no effect on adipokines and IR.
Santos, 2014 [88]	40 W 6 M	40.5	43	Clinical trial	LAGB	16	3	↓	__	__	Adipose tissue loss improved inflammation markers
Lips, 2016 [87]	15 gastric bypass 12 VLCD	52	42.0	Clinical trial	12 VLCD 15 RYGBP	17 20	3	↓	↓	↓ ↑	VLCD is more effective than Roux-en-Y gastric bypass on inflammation

M = men; W = women; VLCD = very low-calorie diet; PRC = protein C reactive; IR = insulin resistance; RYGBP = Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding; LSG = laparoscopic sleeve gastrectomy. ND = not detected. SAA = serum amyloid A.

Table 3
Effect of weight loss on gene expressions.

Authors	Patients	Age	BMI (kg/m^2)	Type of study	Study design	Duration	Weight loss (kg)	Results
Vink, 2017 [93]	25 M 28 W	51.7 50.4	31.5 30.8	Observational. Adipose tissue biopsies and gene expression	LCD; 1250 kcal day for 12 weeks or a VLCD; 500 kcal day	5 weeks 12 weeks	8.1 8.9	Gene expression profile of mitochondrial function, adipogenesis and immunity/ inflammation more strongly upregulated on a VLCD compared LCD.
Marques-Rocha, 2016 [81]	20 M 20 W MetS	48.8	35.4	Randomized clinical trial (genes analysis)	Hypocaloric Mediterranean diet, food questionnaire	2	7.3	Reduction in gene expression of cytokine in white blood cells (IL-6, TNF-alpha, ICAM-1, IL-18, SERPINE1, VCAM-1, GAPDH)
Johansson, 2012 [94]	9	38	43.4	Follow-Up Study Gene Expression Profiling	1. LCD (1200 kcal/d) 2. maintenance	3 than follow up 6 months	18.8	Reduction of the inflammatory gene expression profile,
Siklova-Vitkova, 2012 [95]	48 W obese	35	34.8	Clinical trial Gene expression in adipocytes vs. stroma-vascular cells	VLCD (800 kcal) WS (600 kcal) weight-maintenance diet	1 month 2 month 3 months	7.4 10.6 ___	mRNA expression of adipocyte-produced adipokines (leptin, serum amyloid A, and haptoglobin) decreased during the VLCD and increased during the WS period. Adipokines produced by stromal cell increased.
Pendyala, 2011 [83]	10 W	43.2	35	RNA gene expression profile of cytokines	782 kcal fat, and protein of 25%, 25%, and 50%	1.5	10	Rectosigmoid mucosa, reduction of TNF-α, IL-6, IL-8, IL-1β and MCP-1 concentration.
Clement, 2004 [84]	29 obese	30.0	23.0	Controlled Clinical Trial (genes expression in adipocytes)	VLCD	6	1	Weight loss improve pattern of gene expression in obese subjects expressed mostly in the stroma-vascular fraction of adipose tissue.

M = men; W = women; LCD = low caloric diet; VLCD = very low caloric diet; Mets = metabolic syndrome.

kind of the proinflammatory marker detected is evident: the most have considered only the CRP while only a restricted number evaluated IL-6, and TNF-α. Leptin level decreased after weight loss [24,42,44,49,56,59,65]. Although leptin is not a specific marker of inflammation, is correlated with inflammation, obesity and with mortality risk in healthy people [86]. Some author found an increased plasma level of adiponectin after weight loss [40,47,55,70,76] while other did not [42,56,59,61]. The effect of weight loss on adiponectin secretion still remains controversial. More studies evaluating the level of adiponectin and its isoforms as HMW (high molecular weight) are necessary to understand the effect of diet composition and sex hormones on adiponectin changes after weight loss.

Despite the discrepancies between the study design, the most showed that weight loss, independent of the entity, determined a significant reduction in the proinflammatory markers, an improvement in insulin resistance and clinical outcomes. Conversely, some authors did not find any effect [38,49,73]. The lack of effect of moderate weight loss on the level of inflammatory markers observed by Sola et al. [73] could be related more to the methodology of diet administration (first month on a VLCD and that followed by a low calorie diet 1200–1500 kcal/day for 2 months) and to the small number of patients. The study of Strasser et al. [49] was more oriented to evaluate the metabolism of tryptophan and tyrosine rather than the inflammatory markers. Although the positive results described by the clinical studies (Table 1) the most critical point is related to the modest weight loss during the trials with a mean value of about 8 kg during 5 months, showing a modest adherence of the patients to the diet. Magkos et al. [42] found that a modest weight loss of 5% improved only some metabolic parameters as insulin sensitivity while a more consistent weight loss (16%) downregulated genes expression of inflammatory markers.

The weight loss induced by gastric surgery (Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding or sleeve gastrectomy) determined a greater weight loss 22.9 ± 10,4 in an average time of 7 ± 4 months. All studies reported a significant reduction of inflammatory markers [47,77,78,87–93] (Table 2). Lips et al. [87] compared the effect of VLCD and RYGB on systemic inflammation in women with type-2 diabetes and found that hypocaloric diet (VLCD) was more efficient than gastric by-pass in reducing the inflammatory profile. This can be related more to the metabolic changes induced by diet at cellular level than to the removal of fat mass. In fact, weight loss induced by hypocaloric diet act profoundly on adipocytes increasing the mitochondrial function and regulating the RNA gene expression of cytokines [81,83,84,94,95] while weight maintenance after weight loss restored the initial activity.

Some studies investigated the effect of weight loss on gene expression of adipokines in adipose tissue [81,83,84,94–96] (Table 3) and all studies found a significant reduction of the inflammatory markers after body fat removal.

4. Discussion

An excessive ingestion of calories with food causes the development of white adipose tissue (WAT) with the increase in adipocyte number or size [97] favoring metabolic alterations in patients with chronic diseases, but also in healthy subjects [98]. Adipocytes are not only a reservoir of energy and lipids storage, but they are a great source of a variety of bioactive peptides [99] and adipokines such as leptin, IL-6, TNF-α, resistin, adiponectin [100–103]. The enlarged adipocytes activate the macrophages infiltration in the vascular system of WAT by the secretion of monocyte chemoattractant protein-1 (MCP-1) [104], and increasing insulin-resistance [105] and promotes inflammation [106]. The functional activity of adipocytes and macrophages are integrated. Macrophages express FABP aP2 (also called FABP4) and PPARγ, while adipocytes release TNF-α, IL-6, and MMPs (matrix metalloproteinases, an enzyme which regulates the degradation of extracellular matrix proteins during normal tissue turnover) which are expression of macrophages activity [107]. Mature adipocytes secrete explicitly leptin [108] which is positively correlated with body fat mass [109]. Leptin is a hormone acting on the hypothalamus modulating the satiety center and body weight [110]. The higher levels of plasma leptin observed in obese subjects, are an expression of leptin resistance [111] complicating the efforts to understand the mechanisms predisposing to weight gain. TNF-α is produced prevalently by activated macrophages and contributes significantly to insulin resistance [112] and is higher in obese than in normal weight subjects [113]. IL-6 is released by various tissues in response to multiple stimuli such as inflammation and injury and regulates immune response [114], but is produced prevalently by engorged adipocyte in association with IL-8, Ilβ and MCP-1 [107,115] and is associated with body fat mass [116]. Adiponectin is an adipokine with anti-inflammatory properties [117,118] due to its ability to inhibit the IL-6 and MCP-1 production from adipocytes and this action is mediated reducing the transcription nuclear factor-kB (NF-kB) activity as well as through increasing PPARgamma expression [118]. Adiponectin activity is mediated by the receptors, AdipoR1 and AdipoR2 [119] which are essential in the regulation of inflammation and insulin sensitivity [120]. Adiponectin is deeply involved in the process of mitochondrial biosynthesis and function [121,122] due to the activation of AMPK and SIRT1 expression [123]. On the other side, mitochondrial function is associated with adiponectin synthesis and their dysfunction leads to a reduced adiponectin synthesis [124]. Adiponectin level is low in obese subjects [125] in particular high molecular weight (HMW) adiponectin which is determinant in the development of obesity and linked to insulin resistance [120] and to the incidence of type-2 diabetes [126]. Adiponectin expression is reduced in visceral fat [127] and significantly increased after energy restricted diet in subcutaneous adipose tissue [101]. In obese patients, the mitochondrial oxidative capacity is reduced compared to healthy subjects, independently of adipocyte size [128].

In WAT the presence of smaller and fewer mitochondria is determinant in the regulation of energy production [129]; so that adipocytes have a small, but essential, oxidative capacity. The impaired mitochondrial function in WAT is determinant in the development of obesity and type-2 diabetes in obese ob/ob mice [130] and human obese subjects [131]. Notably, the alteration in mitochondrial DNA in humans is a consequence of diabetes and not of obesity [132] evidencing that the alteration of glucose control is the principal deleterious mechanism on mitochondria. The changes in mitochondrial DNA may be a consequence and not a causal factor in adipose tissue pathologies [133]. In fact, the mitochondria activity increased in adipocytes of db/db mice after the treatment with rosiglitazone, a drug that improves insulin activity and glucose control [134].

In obese patients, the reduction of body fat mass, in particular visceral fat, improves mitochondrial function in adipocytes and decrease cytokines production [135,136] playing an important role in the control of the inflammatory response [136,137], vascular endothelial function [138], and immunity [137].

Body fat represents a concomitant source of reactive oxygen species (ROS) [139] essential in the regulation in adipocyte gene expression, and inflammatory cytokines production [99,139]. Physiological mitochondrial production of ROS in WAT promotes adipocytes differentiation [140] and modulates adipocyte apolipoprotein E (apoE) production, which has the function to facilitate lipid flux [141]. Since that, oxidative stress has high pathophysiological importance in both obesity and diabetes [142].

5. The anti-inflammatory effect of hypocaloric diet

Caloric restricted diets result in a negative energy balance causing body fat loss [143] and the activation of lipolysis [144] necessary to provide energy substrates [145]. The reduced caloric intake is the most critical factor to improve cellular metabolism and mitochondrial function compared to exercise and gastric bypass to induce weight loss over the term [146]. Weight loss induced by calorie restriction diet represents the most effective treatment for patients with metabolic disorders [147] reducing the visceral adiposity, and the incidence of type-2 diabetes, and inflammation [147,148]. Weight loss reduces the adipocytes size and the adipokines synthesis and release [149], with consequent improvement in insulin resistance and in the inflammatory process [150] (Fig. 2).

A modest weight loss of 10% [148] is capable of reducing the serum level of inflammatory markers more than double, reducing the cardiovascular risk factor and increasing serum adiponectin level [76,151]. Weight loss assessed a reduction in insulin level of 25%, MCP-1 of 20% and leptin by 24% strengthening the hypothesis that weight loss is beneficial by reducing the low-grade inflammation [152], and is an activator of insulin sensitivity [31,153–155], particularly the CRP level [156,157]. Low carbohydrates diet is more efficient on metabolic improvement compared to conventional weight loss diet, also after adjustment for weight loss differences [158]. The Mediterranean diet determined a significant reduction in pro-inflammatory cytokine thought a modest weight loss was found (about 2 kg) [38].

In patients with severe obesity, also a robust weight loss after laparoscopic adjustable gastric banding led to a considerable reduction of IL-6 and TNF-α production in abdominal fat, but not in liver tissue [91]. A high body fat loss resulted in a significant reduction in macrophage concentration in WAT [92] and the expression of genes governing the cytokines secretion [159]. However, a healthy diet over a seven years period without weight loss, despite an improvement of endothelial dysfunction, did not affect the inflammatory markers [35]. In conclusion, although the quality of diet is important, as observed in Mediterranean diet program, the reduction of body fat is essential in reducing the inflammatory markers.

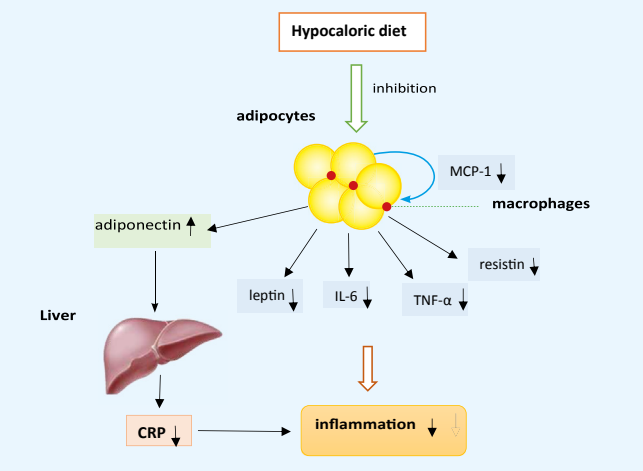

Fig. 2. The anti-inflammatory effect of weight loss. Caloric restriction reduces adipocytes size, metabolism, and inhibits the secretion of specific adipokines such as leptin, IL-6, TNF-α and MCP-1. MCP-1 is responsible of the activation of macrophages infiltration in adipose tissue. Adiponectin, an adipokine with anti-inflammatory effect, increases during weight loss while the secretion of CPR by the liver is reduced. All together, these mechanisms reduce the inflammatory process and decrease the chronic disease evolution.

6. Mechanisms of the anti-inflammatory effect of weight reduction

A direct relationship between fat mass loss and decreased inflammation has been demonstrated [160,161]. Caloric restriction causes changes on gene expression of cytokines reducing the IL-6 mRNA and IL-1B expression and improving insulin sensitivity [75] and regulates gene expression in adipose tissue increasing mitochondrial function [94]. The variation of glucose availability among diet restriction is associated with changes in many genes expression (80–100) in macrophages and adipocytes [162]. The changes in gene expression also involve NF-kappaB activation associated with insulin sensitivity. These genes were downregulated after weight loss [155] and inhibited the expression of cytokines [159].

The amount of total caloric intake with the nutrition has been demonstrated to have similar effects on metabolic changes respect the diet composition. In fact, following an isocaloric diet, low- and high-fat dairy products had no adverse impact on inflammation markers [163]. Although in patients affected by metabolic syndrome exercise training improved some metabolic parameter [164,165], weight loss due to a restricted diet program determined superior effects [166].

7. Weight loss and mitochondria biogenesis

Weight loss has a significant effect on mitochondrial function activating the lipolysis and fatty acids oxidation [167]. Adipocytes are highly sensitive to insulin effect [168] and β-adrenergic system [169]. Importantly, caloric restriction increases the expression of adenosine monophosphate-activated protein kinase (AMKP), the master regulator of cellular energy homeostasis [170], stimulating the mitochondrial biogenesis in adipocytes of WAT [171,172] and improving insulin resistance [173] as observed during starvation [174] or physical activity [175].

The inhibition of AMPK activity is observed during overfeed state and corresponds to the increase in leptin and glucose level [176]. AMPK starts up directly the phosphorylation of metabolic enzymes and indirectly activating the expression of nuclear genes, such as peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), and uncoupling proteins 2 and 3 (UCP2 and UCP3) [170]. PGC-1 signal is also activated by exercise and nutritional factors [177] and plays a central role in the biogenesis and respiration of mitochondria and reduces the inflammatory response to metabolic stress [178]. AMPK–PGC-1-α work together forming an important axis in maintaining the cellular ATP content favoring cell survival under the condition of limited glucose availability [179]. The action of AMPK has been proposed as the mechanism responsible for health and longevity [180]. Calorie restriction increases SIRT1 expression which has a beneficial effect on health and delaying metabolic alteration and chronic disease associated with aging [181]. SIRT1 is enabled by a low plasma level of glucose with consequent activation of fatty acids oxidation and the function of PGC-1α [182]. SIRT1 closely works with AMPK mediating calcium-dependent mechanism which stimulates mitochondrial proliferation and function [183]. Figure 3 importantly, the hypocaloric diet inhibits cytokines release independently of its composition [31]. Jellama et [57] demonstrated that a restricted diet is more efficient than a diet with fish oil to reduce the inflammatory markers levels, showing a superior effect of diet than the moderate intake of fish oil on markers for a low-grade inflammatory.

8. Role of macronutrients

It is essential not only to consider the amount of calorie restriction but also the balance and interaction between

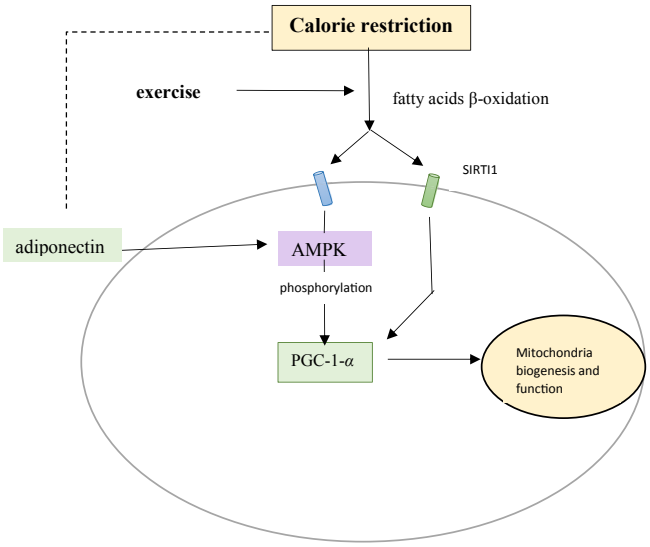

Fig. 3. AMPK and SIRT1 activation by calorie restriction or exercise enhance PGC-1α-expression. AMPK directly interact and phosphorylate PGC-1α and SIRT1-mediated the regulation of PGC-1α activity activating mitochondria biogenesis and function.

macronutrients and calories [185]. The Mediterranean diet is based on recommendations for food consumption [186] encouraging dietary change based on Mediterranean Country nutrition [187] without the determination of total daily calorie intake. Severe caloric restriction, it is difficult to respect by the most patients and probably it is not necessary because the manipulation of macronutrient ratios can bring similar metabolic outcomes.

8.1. Protein

A low protein intake relative to carbohydrates extended the lifespan in flies more than the reduction of total calories ingested, evidencing that the dietary balance is more important than the single nutrient ingestion [185]. Protein intake should have and equilibrate relation with carbohydrates. Diets containing a protein/carbohydrates ratio of 1:13 in males and 1:11 for females in rats achieved the maximal longevity [188]. Diet ad libitum with low-protein, high-carbohydrate content, despite the increased energy intake, has similar metabolic benefits on glucose control compared to a diet with caloric restriction of 40% [189]. The metabolic effect of protein ingestions seems to be correlated to the content of branched chain amino acids which have been involved in the risk of diabetes, obesity and cardiovascular disease [190].

However, in obese subjects a calorie restricted diet with high protein intake (30%) has shown a significant reduction in CRP, IL-6, TNF-α, and PAI-1 [48], metabolic risk factor and adipocytes size [191] without side effects.

8.2. Carbohydrates

The ingestion of adequate carbohydrates is necessary to maintain insulin activity and the metabolic efficiency. An excessive intake of dietary carbohydrates [192,193] and a higher plasma glucose level has detrimental effects on the cardiovascular system and the progression of chronic diseases [194] with increased incidence of all-cause mortality in CVD patients. Hypocaloric diet, both with high compared and low carbohydrates composition, determined the same weight loss and metabolic improvement in type-2 diabetes [195]. Although the glycemic index of the carbohydrates of the diet seemed important in the treatment of metabolic diseases [196], particularly in type-2 diabetes [197], Kristo et al. [198] in a meta-analysis found that comparing the effect of diet with high or low dietary glycemic index and load, unexpectedly, that the higher glycemic index diet resulted in a better glucose control without impact on inflammatory markers. Fasting glucose increased considerably after a diet low glycemic index and high in the legume content [199]. The energy -restricted diet had effects with the same benefit on weight reduction than lowering the glycemic load and glycemic index evidencing that the decrease in the total amount of calories ingested is more beneficial than carbohydrates composition [200]. Furthermore, cortisol metabolism independently of weight loss and may affect metabolic health [201]. In CVD patients, a low-carbohydrate diet is useful in determining weight loss, improvement in inflammatory markers and cardiac function [202].

8.3. Fat

The main effect of a high-fat diet is the downregulation of the genes involved in the control of lipid metabolism and mitochondrial function [203]. High fat diet inhibits adiponectin production and increase in adiponectin receptors, AdipoR1 and/or AdipoR2 expression [204,205] especially in the skeletal muscles, but not in the liver, suggesting a tissue-specific effect on adiponectin and enzyme expression [206]. Nutritional fat ingestion is the most responsible in determining an increase of TNF-α and IL-1β which are inhibited by 74% and 80%, respectively, by polyunsaturated fatty acids, eicosapentaenoic acid by fish oil and alpha-linolenic acid in flaxseed oil [207]. In obese nondiabetic patients, high doses of n-3 PUFA regulated the systemic inflammation [208], however, Telle-Hansen et al. [209] showed that, during the most dietary interventions in obese patients, the different fatty acids administration had no significant effects on inflammatory markers. Despite many studies have demonstrated the impact of omega-6 and 3 on reducing the inflammation [210,211] inflammatory biomarkers [212] and protect against metabolic syndrome also in adolescence [213], no positive effect on inflammation has been observed. It emerges that weight loss is the most consistent determinant of the anti-inflammatory process and that the macronutrients of the diet reduce inflammation synergistically.

9. The dietary approach

Diet restriction is an essential physiologic process to induce health and lifespan [214]. which are correlated with a reduced insulin resistance and increased autopahagy. In mammals, autophagy has a similar role as observed in C. elegans in dietary restriction-mediated lifespan extension. In a meta-analysis, Ajala et al. [215] found that weight loss improved the markers of inflammation in patients with cardiovascular risk independently from the type of diet, both a low-carbohydrate, low-glycemic index, Mediterranean, and high-protein diets. It is essential to specify that a too short period of diet can be ineffective to induce any changes on inflammatory markers as observed by Strasser [49] and what it means caloric restriction because, a severe hypocaloric diet, may be harmful in some specific patient, such as lean persons who have a very low BMI and minimal amounts of body fat [216]. Extremely difficult to standardize dietary studies and to completely control what people are eating, and only a few long-term controlled nutritional studies are available.

10. Conclusions

The critical point in the treatment of inflammation in chronic diseases is represented by a weight loss program by an appropriate diet consisting of energy restriction of about 30% of calories, low fat, moderately high protein intake and carbohydrates until equilibrium.

A low glycemic load is more effective than low fat diet in inducing metabolic improvement [184].The reduction of body fat mass with a hypocaloric diet, also of the modest amount, is powerfully effective in reducing the level of pro-inflammatory cytokines than exercise or supplementation of polyunsaturated fat. A restricted energy diet represents an important physiologic mechanism reducing the inflammatory markers level, more effective than gastric by-pass or using a therapeutic antibody against TNF-α who failed to improve metabolic control and insulin resistance [217,218]. Weight loss following hypocaloric diet reduces plasma level of inflammatory markers activating important enzymatic processes at cellular and nuclear level and mitochondria functions: the metabolic changes suggest that the effect can be related to the body fat loss. Dietary approach represents the first aid to improve the clinical conditions in patients with metabolic syndrome and chronic diseases [157]. However, it is extremely difficult to standardize dietary studies and to completely control what people are eating, and only well conducted long-term nutritional studies are necessary.

Conflict of interest

The author has no conflict of interest to declare.

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