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RESEARCH ARTICLE

DIET, EXERCISEREGIMENS AND MEDICATIONSTHAT ALTER BLOOD LEPTIN, ADIPONECTIN LEVELS AND ADIPONECTIN/LEPTIN RATIO TO PREVENT AND CONTROL CARDIO METABOLIC DISEASES DEVELOPMENT AND PROGRESSION

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Abstract

Objectives: High adiponectin and low leptin levels in serum are associated with less risk of insulin resistance, hypertension, atherosclerosis and a favorable lipid profile. In this systematic review, our objective was to determine effective diet changes, exercise and medications to achieve a favorable adiponectin/leptin ratio that decrease the risk of cardio metabolic conditions.

Methods: After searching the literature in PubMed, MEDLINE, Google scholar and Cochrane library, we included randomized controlled trials and observational studies done on human participants regardless of age, BMI, sex and co-morbid conditions and studies that compared or assessed effects of interventions like diet, exercise or medications for more than two weeks on blood leptin and adiponectin levels. Follow up studies, animal studies and the studies in which adiponectin and leptin levels were not specified were excluded from the review. We screened 118 studies, data was retrieved from 70 studies out of which 36 studies were eligible for quality assessment. We used Cochrane risk of bias tool for randomized controlled trials and new castle Ottawa scale for observational studies for their quality assessment. Finally, we included 22 randomized controlled trials and 2 observational studies.

Findings: The supplements, diet and exercise regimens and medications that were studied, many of them showed desirable changes in adipokine levels. Some of these regimens have not shown changes from baseline.

Conclusions: Exercise, diet modifications and medications like Orlistat, Resveratrol, Pioglitazone should be used to target the adipokine levels to reduce cardiometabolic disease risk and progression.

Introduction:-

Cardio metabolic diseases are a group of conditions which include obesity, insulin resistance and diabetes mellitus, hypertension, atherosclerotic coronary vascular diseases and their consequences on renal, hepatic, neurologic and other systems in the body. These disorders affect millions of people and are a leading cause of worldwide morbidity and mortality. As of 2021, an estimated 463 million people worldwide have diabetes, with the number expected to rise to 700 million by 2045. About 650 million adults are affected by obesityglobally, significantly increasing the

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risk of cardiometabolic complications. Cardiovascular diseases remain the leading cause of death worldwide, accounting for nearly 18 million deaths annually. These staggering statistics emphasize the urgent need for effective prevention, diagnosis, and treatment strategies to address the growing burden of cardiometabolic disorders on healthcare systems and societies worldwide [1].

Adipose tissue is now considered an endocrine organ, secreting leptin, adiponectin, resistin, several cytokines, adipsin, acylation-stimulating protein, angiotensinogen, plasminogen activator inhibitor-1and also produces steroids hormones [2]. It is involved in regulating energy balance and many other physiological functions [3].

Circulating leptin levels reflect long term energy stores in the form of body fat. In addition, leptin levels fluctuate according to changes in calorie intake and circadian rhythm, with a marked decrease during starvation and mid-afternoon and higher during fed state and at midnight. The pulsatile pattern of leptin secretion is similar in obese and lean subjects, but the amplitude is higher in obese subjects. Subcutaneous fat produces more leptin than visceral fat, that justifies higher leptin levels in women compared to men. Leptin levels are also regulated by factors like insulin, glucocorticoids, catecholamine, and cytokines. The binding of leptin to LepRb activates several signalling pathways, including Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) thatplays a crucial role in its ability to regulate energy homeostasis.

Leptin's principal site of action is the brain, specifically in the brainstem and hypothalamus (lateral hypothalamic area and the ventromedial, dorsomedial, ventral pre mammillary, and arcuate (ARC) nuclei), solitary tract and the ventral tegmental area. Leptin acts here to modulate satiety and the control of reward and aversion. The ARC nucleus has neurons that secrete substances that increase appetite like agouti-related protein/neuropeptide Y-containing (AgRP/NPY) and decrease appetite like proopiomelanocortin (POMC). Leptin decreases appetite by inhibiting AgRP/NPY containing neurons. During starvation, as the amount of adipose tissue decreases, the amount of leptin produced and crossing the blood-brain barrier decreases. With increased leptin comes an inhibition of the body's starvation mode, thereby promoting reduced food intake and increased energy expenditure to counteract the current energy surplus [3]. In obese individuals with high leptin levels probably due to leptin resistance do not reduce appetite or increase calorie usage. This can be a therapeutic target for the control of metabolic derangements due to obesity [4].

In the mid-1990s, four independent Japanese or American groups isolated adiponectin (also known as Acrp30/adipoQ/apM1/GBP28) by using diverse techniques [5]. In contrast to leptin, adiponectin level has an inverse relationship with obesity. Adiponectin helps reducing oxidative stress and inflammatory cytokines, increase glucose uptake and improves insulin sensitivity, increase fatty acid and glucose utilization by muscles and reduce lipid content. These effects leads to control of metabolic abnormalities like high BMI, insulin resistance, high blood pressure due to these derangements and prevention of further adverse events. All these effects collectively reduce blood glucose level and improves insulin sensitivity which is beneficial for patients with type 2 diabetes mellitus [6].

Adiponectin also diverts fatty acids from visceral fat to subcutaneous fat, thus helps in overcoming insulin resistance. It controls lipid metabolism by promoting the skeletal muscle transport of fatty acids and β-oxidation, by inhibiting hepatic lipogenesis and by stimulating subcutaneous adipose tissue fat storage [6].

Adiponectin also supresses the expression of various adhesion molecules and receptors on the endothelial cells of blood vessels. This effects prevents adhesion of circulating monocytes and their differentiation into macrophages and cholesterol accumulation, thus prevention of atherosclerosis.

High concentrations of circulating leptin, leptin resistance, and hypoadiponectinemia are associated with obesity, insulin resistance, atherosclerosis and related pathological conditions, suggesting a critical role of these adipokines in the onset and progression of the disease. Targeting these two adipokines with various interventions to increase "adiponectin-leptin ratio" or to decrease "leptin-adiponectin ratio" have recently been studied. In clinical settings, this ratio is a more predictive and reliable biomarker for several metabolic disorders. Therefore, in patients with cardio-metabolic disorders, treatments that reduce leptin and increase adiponectin levels require assessment in detail [7].

Various studies and systematic reviews have been done to study the effects of various diets, exercise, medications and other intervention on adiponectin and leptin levels and adiponectin leptin ratio [8-14]. The results of such studies

are variable. We have found one such systematic review in which the impact of diet and exercise on adiponectin and leptin level has been assessed. But this study had only involved trials with obese and overweight individuals and diet and exercise interventions.

We have conducted this study to assess the effects of diet, exercise and other interventions on blood adiponectin and leptin levels regardless of the BMI and any other active metabolic conditions. The aim of this study is to assess the effectiveness of various interventions on the adiponectin and leptin levels which can be helpful for the prevention and management of cardio metabolic conditions.

Methods: -

Search Strategy:

The current systematic review was conducted in analogous to the PRISMA guideline and the Cochrane Handbook of Systematic Reviews of Interventions. Search strategy PubMed, Google scholar, Cochrane database, Web of Science and MEDLINE were the primary databases searched to identify randomized controlled trials and observational studies, published in last 10 years until June 2023, using dietary interventions, exercise, medications and primary or secondary outcome of leptin, adiponectin levels, and leptin adiponectin ratio or adiponectin leptin ratio either all or an individual outcome. The keywords used for the search strategy included but were not limited to: Leptin, Adiponectin, Diet interventions, Exercise interventions, Insulin resistance, Metformin, Hypoglycemic agents. The review was structured as per the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.

Study Selection:

Inclusion and exclusion criteria were determined after discussion with all the reviewers. The inclusion criteria were as follows: 1) English language; 2) human participants; 3) results that included serum or plasma leptin and/or adiponectin and/or Leptin-adiponectin or adiponectin-leptin ratio. 4) duration of intervention more than 2 weeks and 5) randomised controlled trials and observational studies that compared or assessed effects of diet, exercise or medications on blood leptin and/or adiponectin levels. The exclusion criteria were as follows: 1) no primary studies, 2) non-English languages, 3) animal studies, and 4) studies that assessed the adipokine levels without any interventions.

Screening and data collection:

The search and screening were performed by two independent reviewers and any disagreements were resolved by discussion with another reviewer. Two independent reviewers screened the articles based on titles, abstracts, and key words.

Results:-

Search results:

The selected publications were undergone full text review and data extraction. Data extraction included year of publication, study design, detailed sample size, age, type of intervention (diet, exercise or medication), biomarker levels, statistical analysis and adjustments, results and conclusion.

The systematic review comprised the population of obese, overweight or normal patients with or without cardio metabolic disorders such as type 2 diabetes mellitus, hypertension, chronic renal disease or coronary heart disease. Studies including outcomes related to blood leptin and/or adiponectin levels were included.

Quality Assessment:

Quality assessment for randomized controlled trials was done based on Cochrane risk of bias tool and for observational studies, it was done with the New Castle Ottawa Scale [Table 1 and 2]. According to the Cochrane risk of bias tool, studies with overall risk of bias is low and for observational studies, New Castle Ottava Scale score of ≥ 7 were included in the review. All remaining articles were assessed independently, and any disagreements were resolved by discussion with another reviewer.

Data extraction and synthesis:

Two reviewers independently extracted data from final eligible studies and any disagreements were resolved by discussion with another reviewer. The data describing: 1) study characteristics, including study design and sample

size; 2) participant characteristics, including sex, age, BMI, and comorbidities; 3) Exercise characteristics, including mode, intensity, duration, and frequency; 4) Diet characteristics, including type and duration; 5) Medications affecting leptin and adiponectin levels; 6) outcome variables; 7) preintervention and post intervention means and SDs or mean changes and their SDs or p values.

Included studies

The initial search of the databases of randomized trials and observational studies resulted in 1241 records from PubMed, 2960 records from google scholar, 425 records from Cochrane database and 12 records from MEDLINE. As shown in figure 1, atotal of 118 articles were identified for full-text screening based on our inclusion and exclusion criteria and out of these, 48 articles were removed due to duplication data and other reasons. Of these, 36 articles were assessed for eligibility. After eligibility assessment 24 articles were finally included as they have depicted serum levels of adiponectin, leptin or their ratio or changes in their levels in mean, SD or changes in percentage or p value after the intervention.

Two studies were excluded due to high risk of bias [22,29]. One study was excluded due to short study duration in days [51]. One study was a follow up of RCT few years back, hence it was excluded [37]. Three cross studies were also excluded as the effects of dietary intervention duration could not be studied [17, 18, 47]. One study assessed the effects of environmental pollution, it was also excluded as there was no intervention [45]. Studies in which the parameters values were not depicted appropriately were also excluded [44, 31,27]. One study that calculated only adipose tissue adipokine levels were also excluded [39].

Types of study, intervention characteristics and their outcomes to be included in this study are summarised in table 3.

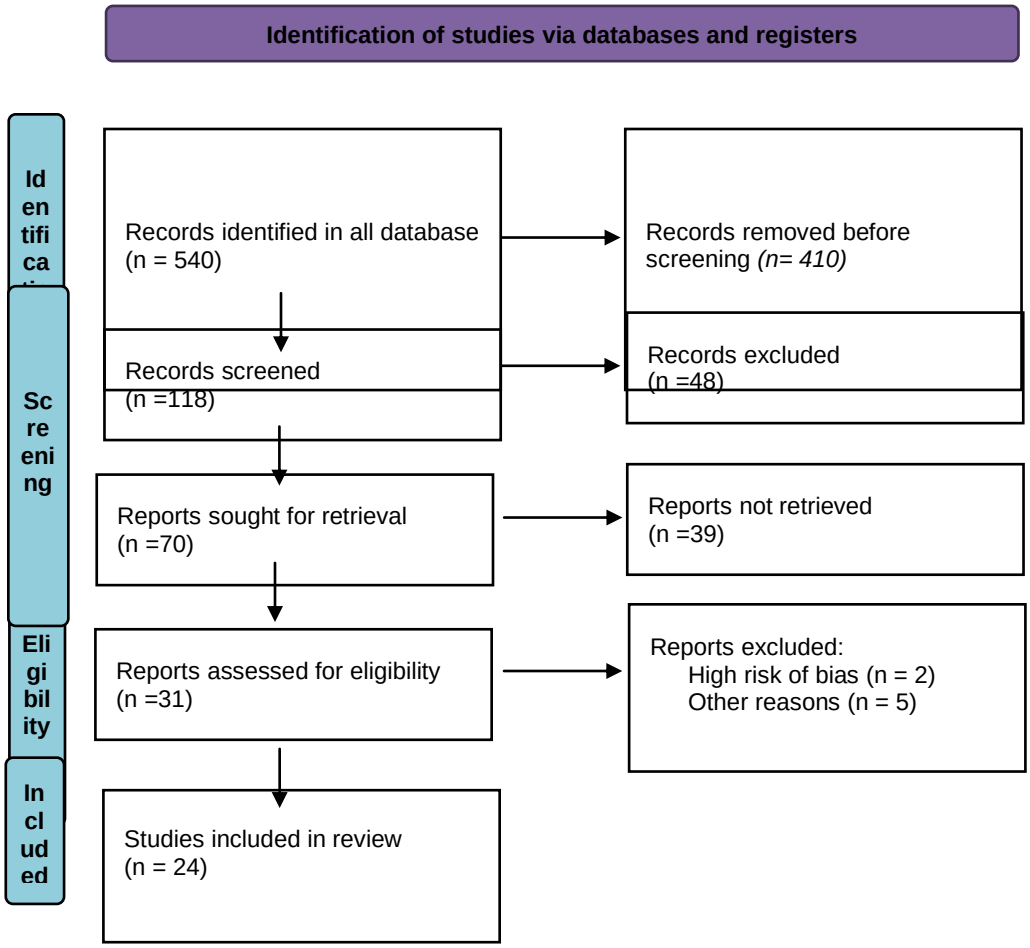

Figure 1:- PRISMA flow diagram of study selection.

Randomised controlled TrialStudy	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
1. Jasminka Z. Ilich et al,March 2022[19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2. Katelyn E. Senkus et al, August 2022[20]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
3. Mozhgan Eskandari August 2020[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4. Jelizaveta Sokolovska et al, 2020[35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5. Ann-Kathrin Lederer et al, September 2022[41]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
6. Deaglan McCullough et al, september 2022[48]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
7. Aleksandra Zebrowska et al, January 2021[49]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8. Justin D. Roberts et al, February 2021[50]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9. Rujira Nonsa-ard et al, November 2022[31].	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10. Ana Serna, et al, September 2021[59].	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
11. Judit Bassols et el, December, 2019[60].	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
12. Seyed Reza Mirhafez et al, June 2019[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
13. John F. Trepanowski et al, December 2017[28]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
14. M. Gorety Jacobo-Cejudo et al, June 2017[25]	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
15. Stefania Mai, may 2017[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
16. Fatemeh Haidari et al, 2017[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
17. Afshin Gharekhani et al. September 2016[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
18. María Angélica et al, May 2016[32].	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
19. Ghazi Racil et al, October 2015[42]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
20. Jie Dong et al, December 2015[36]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
21. Anne K. Swisher et al, October 2015[34]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk

22. Anne Zanchi et al, October 2014[40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
23. Adana A.M. Llanos et al, April2014[27]	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	Low risk	Low risk
24. Mariangela Rondanelli et al, December 2012[61]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
25. Magdalena Mostowik et al, August 2013[38]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
26. Liqing Yu et al, June 2013[29]	High risk	High risk	High risk	Low risk	Low risk	Low risk	High risk
27. Anthony M Belenchia et al, April 2013[23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
28. Rocío Aller, 2023[24]	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
29. J.A. Rausch, 2021[14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 1:- Quality assessment of randomized controlled trials.

Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposures	Outcome of interest not present at the start of the study	Comparable on the basis of design or analysis	Assessment of outcome	Adequate duration of follow up	Adequate completion of follow up	Total score
1. Mohammed Faraz Rafeyel al, May 2022[21]	1	-	1	1	2	1	1	1	8
2. Celestino Sardu et al, September 2019[39]	1	1	1	1	2	1	1	1	9

Table 2:- Quality assessment of observational studies.

Author and Year of publication	Study design and duration	Intervention	Outcome assessed	Mean Value Pre intervention	Mean Value Post intervention	Change in level	p value	Conclusion
Stefania Mai, 2017[16]	RCT 4 weeks	Cholecalciferol 600000 IU	high molecular weight Adiponecti	1.6 ± 0.4	1.5 ± 0.2		p = not significant	

			n mcg/ml					
			Leptin ng/ml	44.1 ± 7.2	31.6 ± 5.9		p <0.05	
			Leptin/ high molecular weight adiponectin	49.1 ± 12.0	24.7 ± 4.2		p < 0.05	
		Placebo	high molecular weight Adiponectin mcg/ml	2.1 ± 0.8	1.9 ± 0.5		p=not significant	
			Leptin ng/ml	41.1 ± 4.6	9.8 ± 4.1		p<0.001	
			Leptin/ high molecular weight adiponectin	37.4 ± 7.4	35.5 ± 9.9		p<0.05	
Jasminka Z. Ilich, 2022[19]	RCT 6 months	Dairy group: 4–5 servings/day of low-fat dairy foods	Adiponectin mcg/ml	12.7 ± 6.5	15.4 ± 5.8		p<0.05	
			Leptin ng/ml	37.8 b ± 19.1	29.5 ± 21.7		p<0.05	
		Supplement group: pills containing 315 mg Ca + 200 IU of vitamin D/day	Adiponectin mcg/ml	11.8 ± 5.9	16.4 ± 9.3		p<0.05	
			Leptin ng/ml	32.5 b ± 19.1	28.9 ± 16.9		p<0.05	
		Placebo pills	Adiponectin mcg/ml	11.7 ± 5.2	17.9 ± 8.5		p<0.05	
			Leptin ng/ml	46.4 ± 34.9	37.9 ± 26.3		p<0.05	
Katelyn E. Senkus, 2022 [20]	RCT 12 months	Exercise only	Adiponectin/Leptin Ratio	-	-		p=0.04	In all groups, 12 months increase in adiponectin, decrease in leptin and increase in A/L ratio is significant in females than in males. (Value of A/L ratio for exercise only group not depicted in the study.)
		Exercise + weight maintenance	Adiponectin/Leptin Ratio	0.327	0.361		p=0.027	
		exercise + weight loss	Adiponectin/Leptin Ratio	0.537	0.511		p<0.001	
Mohammed	prospecti	Before starting	Adiponecti	6.2	8.1		p<0.001	

Faraz Rafey, 2022, [21]	ve observational cohort study, 18 months	Low energy liquid diet. Without Diabetes	n mcg/ml Leptin ng/ml LAR	 92.8 11.7	 42.8 5.6		p<0.001 p<0.001	
		With Diabetes	Adiponectin mcg/ml Leptin ng/ml LAR	4.8 74.9 16	6.0 44.5 6.0		p=0.004 p=0.001 p=0.002	
Anthony M Belenchia, 2013[23]	RCT, 6 months	4000 U Vitamin D3/d	Adiponectin mcg/ml Leptin ng/ml LAR	5.86 +- 0.20 43.5 +- 1.8 7.45 +- 0.02	6.06 +- 0.20 36.7 +- 2.0 6.04 +- 0.02		p=0.447 p=0.043 p=0.009	
		Placebo	Adiponectin mcg/ml Leptin ng/ml LAR	5.88 +- 0.21 43.5 +- 1.9 7.41 +- 0.01	5.90 +- 0.21 44.1 +- 2.1 7.51 +- 0.01		p=0.958 p=0.993 p=0.857	
Rocío Aller, 2023[24]	RCT 3 months	Type P diet-rich in poly unsaturated fat	Adiponectin ng/ml Non T allele T allele Leptin ng/ml Non T allele T allele A/L Ratio Non T allele T allele	 19.10+-- 4.1 10.1 +-3.1 70.9 +- 12.3 75.5 +- 9.1 0.29 +- 0.09 0.13 +- 0.1	 39.1 +- 4.9 16.9 +-- 6.1 45.1 +- 9.5 50.1 +- 9 0.86 +- 0.1 0.33 +- 0.2		 p=0.02 p=0.01 p=0.03	T allele vs Non T allele increase in adiponectin level and AL ratio) (significant increase without T allele)
		type M diet-rich in monounsaturated fat	Adiponectin mcg/ml Non T					

			allele T allele Leptin ng/ml Non T allele T allele A/L Ratio Non T allele T allele	15.9 ± 1.2 11.2 ± 2.9 71.3 ± 9.1 78.3 ± 7.2 0.22 ± 0.08 0.14 ± 0.07	35.4 ± 2.2 15.7 ± 1.3 46.2 ± 8.1 53.4 ± 4.1 0.76 ± 0.1 0.29 ± 0.1		p=0.01 p=0.01 p=0.03	
M. Gorety Jacobo-Cejudo, 2017[25]	RCT 24 weeks	Fish oil, n-3 polyunsaturaye d fatty acid (FOG)	Adiponecti n ng/ml Leptin ng/ml LAR	23.6 ± 20.3 21.7 ± 15.5 1.3 ± 1.2	24.5 ± 13.0 3.9 ± 2.5 0.24± 0.26		p=0.177 p=0.000 p=0.000	
		Placebo	Adiponecti n ng/ml Leptin ng/ml LAR	22.8 ± 10.5 18.4 ± 13.2 0.88 ± 0.68	24.3 ± 13.3 3.5 ± 2.3 0.17 ± 0.12		p=0.563 p=0.000 p=0.000	
Seyed Reza Mirhafez, 2019[26]	RCT 8 weeks	In NAFLD patients: Phytosomal curcumin	Adiponecti n ng/ml Leptin ng/ml LAR	14.35 (7.72) 23.21 (16.93) 1.81 (1.90).	18.23 (9.75) 17.85 (14.11) 1.12 (1.09)		p<0.001 p<0.001 p<0.001	
		Placebo	Adiponecti n ng/ml Leptin ng/ml LAR	11.85 (6.75) 15.01(18.9 2) 1.59 (3.22)	10.87 (4.95) 15.86 (17.06) 1.97 (411.07)		p=0.12 p=0.61 p=0.13	
John F. Trepanowsk i, 2018[28]	RCT 24 weeks	Alternate day fasting. (consuming 25% or 125% of energy needs)	Adiponecti n ng/ml Leptin ng/ml	4321 ± 589 66.2 ± 6.0	5285 ± 620 54.6 ± 6.2		P<0.05 P<0.01	The ADF group and CR group experienced greater reductions over time compared to the control group, but similar reductions
			Adiponecti n ng/ml	4051 ± 373	4730 ± 376			

		Calorie restriction (consuming 75% of needs every day) Control	Leptin ng/ml	73.1 ± 10.2	50.1 ± 7.0			compared to each other.
			Adiponectin ng/ml	3684 ± 600 4228 ± 612	53.3 ± 6.1 63.0 ± 8.5			
			Leptin ng/ml					
Mozhgan Eskandari, 2020[30]	RCT 6 weeks	JW, jump rope exercise + white chocolate supplementation DS, dark chocolate supplementation JD jump rope + dark chocolate C, control	Adiponectin ng/ml			+0.2	p<0.001	
			Leptin ng/ml			-0.03	p=0.003	
			Adiponectin ng/ml			+0.06	p<0.001	
			Leptin ng/ml			-0.01	p=0.021	
			Adiponectin ng/ml			+0.3	p<0.001	
			Leptin ng/ml			-0.09	p<0.001	
			Adiponectin ng/ml			No significant difference	No significant difference	
			Leptin ng/ml					
María Angélica, 2016[32]	RCT 6 months	Orlistat + Resveratrol	Adiponectin mcg/ml	7.75 ± 4.52	8.41 ± 2.77		p=0.437	No significant differences among the groups were observed for adiponectin. The serum leptin concentrations in the O-R group decrease significantly compared to the placebo. Leptin adiponectin ratio significantly decreased in O-R group. (Values are not given in the article)
			Leptin ng/ml	32.6 ± 20.4	27.1 ± 10.2		p=0.007	
			LAR				p<0.05	
		Resveratrol	Adiponectin mcg/ml	7.76 ± 3.52	8.30 +-2.74		p= not significant for all 3 parameters.	
			Leptin ng/ml	25.2 ± 16.9	26.3 ± 10.4			
			LAR					
		Orlistat	Adiponectin mcg/ml	6.97 ± 4.97	8.89 +-3.38		p= not significant for all 3 parameters	
			Leptin ng/ml	25.3 ± 15.2	23.5 ± 12.7			
			LAR					
		Placebo	Adiponectin mcg/ml	7.15 ± 3.53	8.15 +-3.09		p= not significa	

			Leptin ng/ml LAR	24.7 ± 9.65	25.5 ± 10.1		nt for all 3 parameters	
Fatemeh Haidari, 2017[33]	RCT 8 weeks	400mg green coffee bean extract	Adiponectin mcg/ml Leptin ng/ml	1.07±7.7 8.06±29.8	2.03±8.9 8.31±22.7		p=0.001 p=0.001	
		Placebo	Adiponectin mcg/ml Leptin ng/ml	1.05±7.6 9.05±30.4	2.8±7.8 7.32±27.7		p=0.08 p=0.04	
Anne K. Swisher, 2015[34]	RCT 12 weeks	All breast cancer survivors. With coaching, 150 min per week of moderate-intensity aerobic exercise, defined as rating of perceived exertion of 11–14.	Adiponectin ng/ml Leptin ng/ml	17.8 (16.8, 19.9) 39.7 (26.3, 66.1)	17.5 (13.5, 25.8) (14.7, 47.3)		p=0.58 p=0.26	Data are presented as median (interquartile range). 54 % (n=13) of women in the intervention group lost at least 1 kg or more of body weight and 30 % (n=10) in the control group gained more than 1 kg of body weight. This study investigated the association of BMI with changes in blood adipokines. Serum leptin, adiponectin and leptin/adiponectin ratio were significantly correlated to BMI in the intervention group (r=0.6469, p=0.0314 and r= −0.7924, p=0.0036, r=0.1165, p=0.0137), respectively.
		Written materials about healthy eating for cancer survivors and suggestions on ways to achieve regular physical activity, without coach.	Adiponectin ng/ml Leptin ng/ml	15.4 (14.4, 23.7) 47.9 (26.3, 53.0)	16.1 (14.0, 26.4) 40.5 (16.5, 69.9)			
Jelizaveta S okolovska, 2020[35]	RCT 4 months	Interval walking. 60 min training with 3 min intervals of fast and slow walking 3 times a week.	Adiponectin mcg/ml Leptin ng/ml LAR	7.11 ± 5.74 11.43 ± 9.07 2.42 ± 3.01	7.79 ± 3.57 10.59 ± 7.3 1.38 ± 0.96		p=NS p=NS p=0.01	
		Control	Adiponecti	7.86 ± 3.87	7.49 ± 5.23		p=NS	

			n mcg/ml Leptin ng/ml LAR	 11.73 ± 6.36 1.85 ± 1.51	 12.81 ± 7.05 2.8 ± 2.28b		 p=NS p=0.06	
Jie Dong, 2015[36]	RCT 6 month	Regular protein diet supplement with ketoacids.	Adiponectin mcg/ml Leptin ng/ml LAR	15.6 (7.7–22.4) 21.9 (16.8–31.1) 1.5 (0.7–3.1)	18.3 (7.4–31.3) 24.6 (15.9–36.2) 1.3 (0.6–4.0)		p=0.01 p=0.24 p=0.75	adiponectin decreased without intervention, Intergroup adiponectin p= 0.01, intergroup L/A ratio p<0.001
		Protein diet without keto acids	Adiponectin mcg/ml Leptin ng/ml LAR	16.8 (11.0–29.8) 23.6 (14.9–31.5) 1.2 (0.8–2.0)	12.6 (8.0–25.0) 23.0 (16.7–31.4) 1.7 (0.8–2.9)		p=0.03 p=0.63 p=0.008	
Magdalena Mostowik, 2013[38]	RCT 1 month	omega 3 PUFA vs Placebo	Adiponectin Leptin A/L ratio			+12.7% -16.7% +33.3%	p=0.0042 p<0.0001 p<0.0001	Adiponectin and A/L ratio increased after PUFA supplementation compared to placebo.
Anne Zanchi, 2014[40]	Randomised cross over study 16 weeks	All patients on hemodialysis or peritoneal dialysis Pioglitazone	Adiponectin mcg/ml Leptin ng/ml LAR		49.1 +- 9.0 36.7+- 15.9 10^{-3} +- 0.25 * 10^{-3}		p=0.04 p=0.04 p= 0.008	Under pioglitazone, plasma leptin concentrations significantly decreased, whereas plasma adiponectin significantly increased, thus resulting in a dramatically suppressed L/A ratio
		Placebo	Adiponectin mcg/ml Leptin ng/ml LAR		22.6 +- 5.1 54.0 +- 16.5 3.63 * 10^{-3} +- 1.04 * 10^{-3}			
Ann-Kathrin Lederer, 2022[41]	RCT 4 weeks	Vegan diet	Adiponectin mcg/ml Leptin	13.4 +- 6.9 17.3 +-	15.5 +- 7.6 15.8 +-		p=0.06 p=0.16	

			ng/ml	11.2	11.5			
		Meat rich diet	Adiponectin mcg/ml	12.3 +- 7.2	11.6 +- 7.3		p=0.4	
			Leptin ng/ml	16.6 +-14.7	16.9 +- 14.8		p=0.39	
Ghazi Racil, 2016[42]	RCT 12 weeks	High-intensity interval training only (HIIT)	Adiponectin mcg/ml	7.5 ± 1.5	9.4 ± 1.7		p<0.05	
			Leptin ng/ml	20.2 ± 2.6	17.3 ± 1.8		p<0.05	
			LAR	2.8 ± 0.6	1.9 ± 0.4		p<0.01	
		Combined plyometric exercise and high-intensity interval training (P+HIIT)	Adiponectin mcg/ml	8.0 ± 1.3	10.5 ± 1.7		p<0.05	
			Leptin ng/ml	17.6 ± 2.3	13.5 ± 2.0		p< 0.05	
			LAR	2.3 ± 0.5	1.3 ± 0.3		p<0.001	
		No-exercise control.	Adiponectin mcg/ml	7.1 ± 1.1	7.4 ± 0.7			
			Leptin ng/ml	18.5 ± 2.0	18.9 ± 1.8			
			LAR	2.7 ± 0.6	2.6 ± 0.3			
Afshin Gharekhani, 2016[43]	RCT 4 months	1800 mg of omega-3 fatty acids	Adiponectin ng/ml	24.79 ± 23.62	27.64 ± 22.64		p=0.70	The mean differences of serum leptin, adiponectin, and were similar between the two groups following 4 months of the intervention period.
			Leptin ng/ml	17.62 ± 19.70	25.05 ± 23.60		p=0.17	
			LAR	5.061 ± 8.507	4.687 ± 10.965		p=0.64	
		Placebo	Adiponectin ng/ml	15.08 ± 14.37	27.49 ± 28.35		p=0.35	
			Leptin ng/ml	25.40 ± 28.61	20.66 ± 25.69		p=0.88	
			LAR	3.765 ± 5.037	6.027 ± 12.550		p=0.60	
J.A. Rausch, 2021[46]	RCT 8 weeks	1.5 gm omega-3 eicosapentaenoic acid (EPA) and 1 gm docosahexaenoic acid (DHA)	Adiponectin ng/ml	17.2 (8.7)	10.7 (8.8)			Between groups adiponectin increase at 8 weeks p = 0.03
			Leptin ng/ml	56.2 (14.2)	60.3 (13.1)			
			LAR	LAR- 6.6 (1.5)	5.6 (1.5)			
		Placebo	Adiponectin ng/ml	27.2 (6.8)	32.9 (5.2)			

			Leptin ng/ml LAR	79.1 (16.9) 5.5 (1.1)	77.2 (15.7) 5.3 (1.3)21			
Deaglan McCullough, 2022[48]	RCT 8 weeks	High carbohydrate, lower fat (HCLF) diet	Adiponectin mcg/ml Leptin ng/ml LAR	2.01 (2.09) 1.31 (0.71) 0.37 (0.41)	2.12 (1.85) 1.07 (0.86) 0.31 (0.7)		p=0.079 p=0.285 p=0.029	The leptin/adiponectin ratio (LAR) was significantly higher at baseline (p = 0.007) and week 4 (p = 0.010) in the LCHF group compared with the HCLF group. Post-hoc analysis reported LAR levels to be significantly lower at week 4 (p = 0.049) and week 8 (p = 0.004) compared with baseline in the LCHF group. In the HCLF group only week 4 showed a decreasing trend (p = 0.053) compared to baseline.
		Low carbohydrate high fat (LCHF) diet	Adiponectin mcg/ml Leptin ng/ml LAR	2.69 (3.27) 3.98 (1.86) 1.70 (2.63)	3.19 (3.33) 1.20 (2.42) 0.70 (1.37)		p=0.964 p=0.001 p=0.001	
Aleksandra Zebrowska, 2021 [49]	RCT 3 weeks	omega free fatty acids extract(90% of ω-3 PUFA (142 mg of EPA, 267 mg of DHA), 12 mg of vitamin E and 5 µg of vitamin D)	Adiponectin mcg/ml Leptin ng/ml	23.8 ± 8.5 3.3 ± 1.9	31.4 ± 7.7 2.7 ± 1.0		p<0.01 p<0.01	
		Placebo	Adiponectin mcg/ml Leptin ng/ml	28.8 ± 8.5 2.6 ± 0.4	30.1 ± 13.5 2.7 ± 0.3			
Justin D. Roberts, 2021[50]	RCT 8 weeks	dGTE,decaffeinated green tea extract (580 mg·d −1 dGTE, delivering 400 mg·d −1 EGCG, caffeine trace (≤0.5%))	Adiponectin mcg/ml Leptin ng/ml	9.06 ± 1.16 17.59 ± 4.28	9.39 ± 1.45 17.46 ± 3.75			Mean adiponectin levels for dGTE+ were significantly greater compared to PL at baseline (p = 0.036), week 4 (p = 0.021) and week 8 (p = 0.049). No other main effects were found for all variables.
		dGTE+,	Adiponecti	11.17 ±	11.08 ±			

		decaffeinated green tea extract and quercetin (50 mg·d −1) and α-lipoic acid (LA; 150 mg·d −1)	n mcg/ml Leptin ng/ml	1.40 24.66 ± 5.50	1.50 25.21 ± 5.89			
		Placebo	Adiponectin mcg/ml Leptin ng/ml	5.94 ± 1.50 15.88 ± 3.83	5.82 ± 1.35 18.78 ± 3.61			

Table 3:- Types of study, intervention characteristics and their outcomes.

Discussion:-

In this systematic review of randomized controlled trials and observational studies, we found a variety of results. Various dietary patterns, diets, exercise and medications affect leptin and adiponectin levels. Many of these effects are significantly effective for increasing blood adiponectin and decreasing leptin levels, which can be taken into consideration for therapeutic purpose. In vitamin D deficient and obese patients with average BMI of 42.7 ± 1.3 kg/m2, Cholecalciferol 600000 IU supplementation was given dailyfor 4 weeks, which has demonstrated significant reduction in leptin level and leptin/adiponectin ratio [16]. Another study with daily supplementation of 200 IU of vitamin D along with 315 mg of calcium also demonstrated reduction in leptin level and increase in adiponectin level significantly at the end of six-month trial [19]. Both of these studies have also given emphasis on calories restriction, aerobic exercise and weight reduction in all study subjects. This can be interpreted as vitamin D and calcium supplementation along with hypocaloric diet and weight reduction provides greater benefit for achieving favourable adipokine profile than without these supplementations. One such study that gave vitamin D3 4000 IU to obese adolescents for six months, observed a decrease in leptin to adiponectin ratio [23]. There were no significant changes in leptin and adiponectin levels. This study did not include participants involved with weight reduction, calorie restriction or exercise. May be less significant changes in leptin adiponectin ratio can be due to absence of associated weight reduction and calorie restriction strategies.

Rocio Aller et al had studied the effects of diets rich in polyunsaturated fat and monounsaturated fat for 3 months. They divided the study group into two genetic profiles in each intervention [24]. Adiponectin is encoded by the ADIPOQ gene, which is located on chromosome 3 at q27 and has three exons [52]. Among all the known ADIPOQ genetic variants studied, one common genetic variant of the ADIPOQ gene is rs822393 (-4522C/T), which is located in the proximal promoter region. some SNPs of the ADIPOQ gene have been demonstrated to interact with dietary intake of fat, and this interaction modifies adiponectin levels [53]. With the use of RT-PCR test, they generated genetic sequence of this particular gene from all the participants' blood and divided them into non-T allele and T allele groups. The study showed significant increase in adiponectin and adiponectin/leptin ratio and decrease in leptin levels in participants with non-T allele genetic profile in both diet groups. Absence of T allele variant is associated with profound effects on adipokine profile after dietary changes.

One study by Jacobo-Cejudo et al has shown a significant reduction in leptin and leptin/adiponectin ratio after 24 weeks of 520 mg of n-3 polyunsaturated fatty acid supplementation in patients with type 2 diabetes mellitus [25]. In this study similar results were observed with placebo group. This study included diabetic patients and majority were taking Metformin plus Glibenclamide or Metformin alone. The findings in the study could be due the effects of these medications.

Omega 3 PUFA 1 gm/day also has favourable effect on adipokine profile. Similar findings were observed by Mostowik M. et al [38]. All participants in this study had CAD and had undergone PCI. One study by Gharekhani A. et al with 1800 mg/day of omega 3 PUFA supplementation for four months has not shown similar findings [43]. In this study all patients were on haemodialysis. Omega 3 PUFA has shown to have beneficial effects on the adipokine profile but in this study, the different results could be due to chronic renal dysfunction and haemodialysis therapy.

Decreased renal clearance and altered secretory patterns of adipocytokines lead to the accumulation of these cytokines, playing a crucial role in the metabolic derangements [56]. Rausch J. A. et al had observed an increase in adiponectin but no significant changes in leptin levels after supplementation of 1.5 gm omega-3 eicosapentaenoic acid and 1 gm docosahexaenoic acid for four weeks compared to placebo [46]. This study had included participants from a wound care centre with chronic inflammatory conditions. This clinical profile may have contributed to these findings. One study was conducted on marathon runners to observe the effects of omega 3 fatty acid with 142 mg eicosapentaeonic acid (EPA) and 267 mg of docosahexaenoic acid (DHA) for 3 weeks by Zebrowska A. et al [49]. It showed significant increase in adiponectin and decrease in leptin levels compared to placebo.

Effects of 400 mg green coffee bean extracts with 180 mg of chlorogenic acid, and caffeine of less than 0.01% has also been studied that showed significant increase in adiponectin and decrease in leptin after 8 weeks compared to placebo [33]. All participants were on 25% energy restricted diet in this study. One trial was conducted to study the effects of -epigallocatechin−3-gallate (EGCG), decaffeinated green tea extract (dGTE) (delivering 580 mg per day dGTE, 400 mg/day epigallocatechin−3-gallate (EGCG), caffeine trace (≤0.5%) and dGTE plus quercetin (50 mg per day) plus α-lipoic acid 150 mg per day on blood adiponectin and leptin levels compared to placebo. This study by Roberts J. D. et al had shown a significant effect of dGTC with lipoic acid on increasing adiponectin levels [50].

Mirhafez S. R. et al has conducted a study in patients with non-alcoholic fatty liver disease. They gave phytosomal curcumin, an active phytochemical compound of turmeric, as a supplementation for 8 weeks. They found a significant reduction of leptin and leptin/adiponectin ratio and an increase in adiponectin levels at the end of study in patients taking this compound compared to placebo [26]. Increase in adiponectin level could be due to downregulation of genes producing inflammatory markers (NF-κB, IL-6, and TNF-α) [54].

Dong J. et al has observed that regular protein diet if supplemented with keto acid showed a reduction in leptin adiponectin ratio compared to protein diet alone [36]. Keto acids have favourable effect on adipokines, inflammatory markers and improve insulin sensitivity. All participants in this trial had CKD and some were on dialysis therapy.

Effects of low energy liquid diet on patients with and without type 2 diabetes mellitus has been studied by Rafey M. F. et al [21]. As per their findings, after starting this diet for 18 months, adiponectin level was increased and leptin and leptin/adiponectin ratio was decreased. The magnitude of these changes were higher and more significant in patients without diabetes. Diabetes mellitus is a metabolic abnormality due to insulin resistance. These changes may have affected the effects of the diet intervention due to insulin resistance and derangements in fat metabolism compared to non-diabetic patients.

Various dietary pattern changes have also showed promising effects on adipokine levels. Trepanowski J. F. et al has studied alternate day fasting and calorie restriction for 24 weeks [28]. They have shown significant reduction in leptin levels in alternate day fasting and energy restriction group compared to control group. Adiponectin levels were not significantly affected by these interventions.

Lederer A. K. et al had observed in their trial that, consuming vegan diet for 4 weeks showed significant increase in adiponectin levels especially in women and increase in leptin after eating meat rich diet for the same duration especially in men [41]. Meat rich diet is believed to be associated with inflammatory activity, after removing meat and using plant based diet may reduce inflammatory process and increase in adiponectin [55].

Two type of diets containing High carbohydrate low fat (HCLF) and Low carbohydrate high fat (LCHF) had been studied for their effects on blood adipokine levels by McCullough D. et al. They found LCHF diet had shown significant reduction in leptin levels and leptin adiponectin ratio at the end of 8 weeks [48]. HCLF diet included approximately 333 g and 267 g of carbohydrate, 55 g and 45 g of protein and at most 97 g and 78 g of fat per day and LCHF diet consisted of ≤50 g of carbohydrate and increased the amount of fat consumed while eating similar amounts of protein to the HCLF per day. Diet that improves insulin sensitivity, improves adipokine profile [57]. LCHF diet has shown improvement in insulin sensitivity in other studies too [58]. This may have contributed to reduced leptin levels in this study.

Senkus K. E. et al had studied effects of exercise alone and with and without weight reduction on adiponectin/leptin ratio [20]. They found significant increase in adiponectin/leptin ratio in all three groups but the magnitude was highest with weigh reduction. Along with exercise, weight reduction has strong and favourable effects on adiposity markers

than exercise alone. Also, the ratio was higher in females in all groups after 12 months as compared to males. This could be duty higher level of subcutaneous fat in females and probably hormonal effects.

Another trial studied the effects of Jump rope exercise plus white chocolate supplementation, dark chocolate with and without jump rope exercise intervention on adipokines [30]. They concluded that jump rope exercise if combined with dark chocolate supplementation showed more significant reduction in leptin and increase in adiponectin.

Swisher A. K. et al in their study showed that 150 min per week of moderate intensity aerobic exercise for 12 weeks, in breast cancer survivor patients, caused no significant changes in leptin and adiponectin levels as compared to patients who were not being coached this exercise regimen [34]. They observed a decrease in the BMI of participant in both groups and they have shown correlated changes in leptin and adipokine levels.

Another intervention study of interval walking of 3 min of alternate fast and slow walking, in diabetic patients, three times a week for 4 months by Sokolovska J. et al has showed a significant reduction in leptin adiponectin ratio compare to the group without intervention [35].

High intensity interval training alone and if combined with polymeric exercise has significantly caused increase in adiponectin and decrease in leptin level and leptin adiponectin ratio compared to no exercise at all [42]. This study done by Racil G. et al shows positive effects of these intervention for the prevention of cardio metabolic conditions.

Angelica M. et al has studied the effect of Orlistat 120 mg and Resveratrol 100 mg combined and individually on levels of adiponectin and leptin [32]. Both these medications, when combined, showed significant decrease in leptin adiponectin ratio and leptin levels compared to placebo and individual drug therapy. They may have synergistic effects on body fat reduction and adipokine levels which has led to significant changes in leptin adiponectin ratio in this study.

Pioglitazone 45 mg daily for 16 weeks was given to patients with non-diabetic end stage renal disease on dialysis therapy, has showed significant increase in plasma adiponectin and decrease in leptin and leptin adiponectin ratio [40]. These effects could be due to reduction in visceral fat.

Conclusion:-

In this review we concluded that various supplementations like vitamin D, omega 3 PUFA, phytosomal curcumin and keto acids have beneficial effects on adipokine profileS except with inflammatory conditions. Various exercise interventions, vegan diet, LCHF diet and low energy liquid diet are also associated with reduced cardiometabolic risk as they directly affect BMI. Orlistat combined with Resveratrol has also shown promising effects like Pioglitazone therapy.

Limitations:

We have studied majority effects of diet and exercise on adipokine levels. Other medication effects should also be reviewed in depth regarding changes in adipokine levels with their use.

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