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Relation Between Serum Irisin and CRP Levels in Moderate to Severe Atopic Dermatitis Patients

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Abstract

BackgroundPeople who are genetically predisposed to atopic dermatitis as well as those who are exposed to external triggers are more likely to acquire the condition. An epidermal barrier deficiency and immunological dysregulation are regarded to be the root causes of Alzheimer's disease (AD). When inflammation occurs, the liver produces CRP, a pentameric protein that rises in concentration. There are 112 amino acids in Irisin, which is a protein. Skeletal muscle, heart muscle, liver, pancreas, salivary gland, connective tissue, sweat glands, subcutaneous adipose tissue, and the nerve sheath all produce this substance when they are used for muscular contraction and movement. New myokine might reduce obesity and enhance glucose utilisation. Some of the positive benefits of exercise, such as weight reduction and thermoregulation, may be mediated by this substance in humans. Irisin serum levels in patients with moderate and severe atopic dermatitis were assessed in this research, with the goal of determining whether there was a correlation between CRP levels and disease activity and inflammation. Methods: Thirty people with Alzheimer's disease participated in this research. 20 healthy people of the same age and sex were also included in the study as an additional control group. In addition to a thorough clinical and dermatological assessment, each participant in the study received a full medical history. All patients were picked from Benha University Hospitals' Dermatology Outpatient Clinic. Slight, moderate, and severe cases were classified based on their SCORAD scores. Research involving human subjects at Benha Faculty of Medicine was given the go light by the institution's local ethics committee. Before any samples were collected at the Clinical and Chemical Pathology Department Faculty of Medicine Benha University, informed permission was acquired from each participant. It was shown that Irisin and CRP had a negative relationship, as Irisin had a substantial negative correlation with SCORAD whereas CRP had a significant positive connection with SCORAD, according to the findings of this research There is some evidence to support the idea that CRP may be used to assess the severity of AD, and that Irisin may be able to lessen the disease's effects. CRP and Irisin may be used as indicators of the severity of Alzheimer's disease (AD). Also, obesity, which lowers Irisin levels, may put people at risk for Alzheimer's disease.

Key words: Serum Irisin, CRP, Atopic Dermatitis**.**

1. Introduction

Atopic Inflammatory skin disease dermatitis (AD) is characterised by itching, dry skin, and inflammation, as well as exudation. AD is commonly linked to a personal or family history of allergic illnesses (1).

Even though C-reactive protein (CRP) is a non-specific marker of inflammation, it increases in proportion to the degree of tissue damage and inflammation. An ideal tool for monitoring illness progression, it has a half-life of six to eight hours (2).

Adult chronic AD patients' CRP levels may be higher than those of matched controls, but this has not yet been shown to be a reliable indicator of the severity of the illness (3).

Obesity is a medical condition characterised by an abnormal accumulation of body fat to the point that it poses a risk to one's health, including a decreased lifespan and an increased risk of health issues (4). In order to be termed obese, one must have a body mass index (BMI) of more than 30 kg/m2, which is the weight divided by the square of the height (5). Instead of using BMI for newborns and children, doctors use to growth charts developed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) (6).

In a pathogenic perspective, the positive link between AD and obesity might be viewed in two ways. AD is a result of a dysfunctional immune system and an overly sensitive immune system, both of which are brought on by an obese state. Second, both AD and obesity are caused by a sedentary lifestyle and/or poor dietary habits, and this is an epiphenomenon (7).

In the study of obesity-related metabolic and vascular illnesses, adipokines and Myokines have been shown to be connected to adipocyte-secreted proteins (i.e., adipocyte-secreted proteins) (8).

Peptide (myokine) Irisin is the result of the proteolytic processing of the product of type III domain-containing 5, a type I membrane protein, into a new muscle-secreting peptide. Irisin has the potential to reduce obesity and enhance glucose metabolism, according to preliminary studies (9).

Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC1-) regulates this enzyme, which has been postulated to mediate the positive effects of exercise on metabolism by boosting uncoupling protein 1 levels and triggering adipocyte browning and thermogenesis. Irisin exposure may stimulate brown adipose tissue cells to improve metabolic balance in this scenario (10).

Irisin levels have been reported to be positively associated with obesity-related indicators including body mass index (BMI) (11).

Patients with moderate to severe atopic dermatitis were recruited for this research, which aimed to determine the blood level of Irisin and determine whether or not CRP levels were associated with disease activity or inflammation.

2.Patients and Methods

Type The present research was a case-control investigation.

Participants in the Research:

Between November 2019 and March 2020, researchers at Benha University Hospitals recruited 50 patients from the Dermatology, Andrology, and Venereology Outpatient Clinic.

Those who participated in the study were divided into two groups:

Patients with atopic dermatitis were divided into two groups (AD).

Group II: A control group of twenty people of similar ages and sexes who seemed to be in good health.

Dermatology, Andrology, and Venereology Department performed a clinical evaluation. The Clinical Pathology Department performed the serological evaluation.

Criteria for Inclusion:

Patients with moderate to severe Alzheimer's disease (SCORAD) (12).

Diagnosis of Alzheimer's disease based on the Hanafin and Rajka diagnostic standard:

Three or more of the following must be present:

 Pruritus.

There are distinct differences between adults and children when it comes to the development of Flexural Lichenification.

Dermatitis that recurs often or is chronic in nature.

A history of atopy in one's family (asthma, allergic rhinitis, atopic dermatitis).

Three or more of the minor characteristics listed below are required:

 Xerosis.

Hyperlinearity of the palms with keratosis pilaris.

Type I skin test response (immediate).

Increased serum IgE levels.

Initiation at a young age.

Impaired cell-mediated immunity and a proclivity for skin infections (particularly those caused by Staphylococcus aureus and Herpes simplex).

A proclivity towards non-specific dermatitis of the hands or feet.

Eczema of the nipples.

 Cheilitis.

Chronic conjunctivitis.

Infraorbital fold of Dennie and Morgan.

 Keratoconus.

Cataracts in the anterior subcapsular region.

Darkening of the orbit.

Facial erythema and pallor.

A white-flowered pityriasis.

Neck folds in the anterior region.

When you sweat, you get an itchy sensation.

Wool and lipid solvent intolerance.

Accentuation in the periofollicular region.

Food sensitivity.

Environmental and emotional variables have a significant impact on its course.

Delay in the blanching of the white dermis

The following are the criteria for exclusion:

Patients who met any of the following criteria were ruled out of the study:

Type 1 diabetes (T1DM) had greater levels of Irisin than controls (13) but lower levels of Irisin than controls (14) in comparison to people with type 2 diabetes (T2DM).

Patients with fatty liver disease had lower serum Irisin levels than healthy people (15), indicating that the liver is overworked.

Chronic kidney disease patients had considerably lower Plasma Irisin levels, a marker of renal illness (16).

cardiovascular disease since risin levels are much lower in individuals with cardiovascular disease (17).

CRP levels are known to be affected by past illnesses (18).

Those who had been on systemic or topical medication for a month or more before the research were excluded.

Concern about morality:

All participants signed an informed consent form. The study was authorised by the Benha Faculty of Medicine's ethical committee for research involving human participants.

Methods:

The following procedures were performed on all patients.

- Detailed history: -

Details about a person's personal life include the person's name and age as well as their sex and marital status.

History of atopic dermatitis and associated skin illnesses, including the onset, course, and duration of AD, as well as past therapy.

History of the AD family.

Medications (kind, dosage, and duration) used in the past.*

An in-depth study of the body:

Adult BMI is calculated as follows: BMI= body weight (kilogrammes) divided by height squared (metres) (19), and CDC Growth Charts are used for children and babies. https://www.infantchart.com/child/childrenstatureage.php

dermatological examination and clinical diagnosis of moderate and severe atopic dermatitis based on a measure created by SCORAD (SCORAD index) (20). Atopic dermatitis severity is most often assessed using this grading system, which is the most widely used. To assist standardise the evaluation of atopic dermatitis

and to aid in the interpretation of therapy research, this test is utilised.

The SCORAD Index is a sum of three subscores, each of which has a specific value.

Based on bodily surface area and the 'Rule of 9', A is the extent score.

Criteria should be broadened:

Before the age of two, the rule of 9: cervical predominance (fig.1).

- Rule of 9 in adults and older children. (fig.2)

Practicing grading:

When drawing the lesion spread on the assessment sheet, it is best to do so before doing the computation.

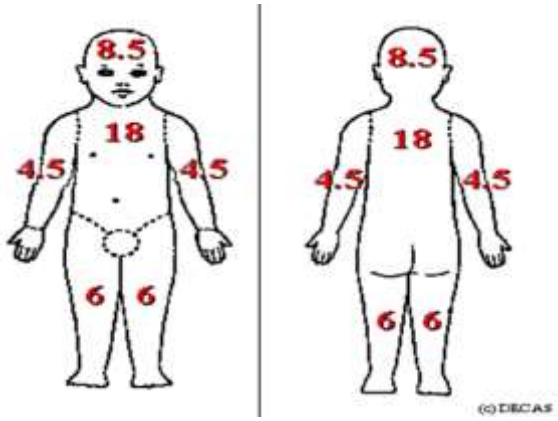

Figure (1): The rule of 9 before the age of 2 years [21].

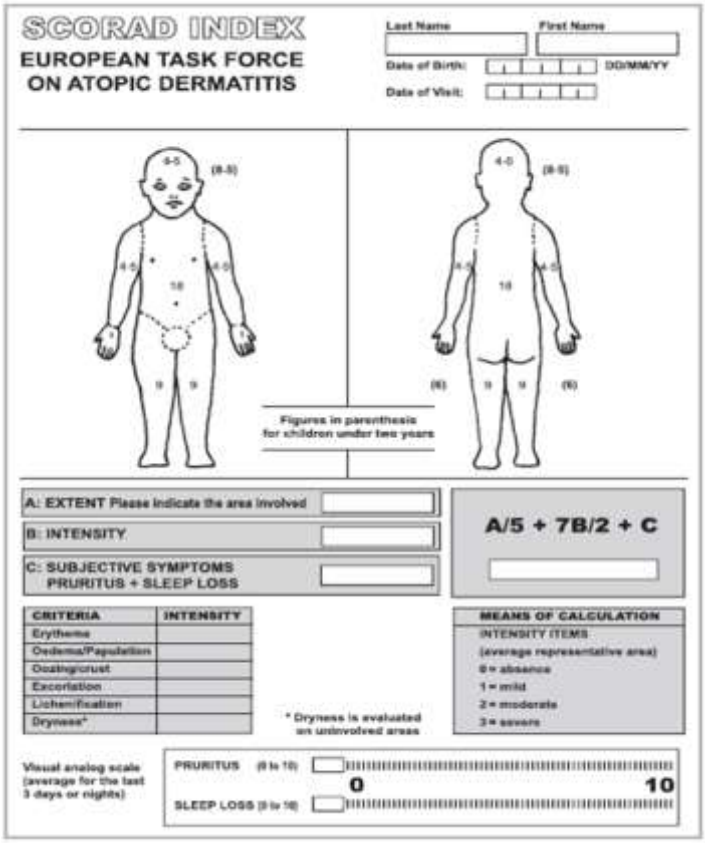

Figure (2): The rule of 9 in adults and older children

B = Intensity score based on 6 clinical findings in atopic dermatitis, namely erythema, edema or papulations, oozing or crusting, excoriation, lichenification, dryness, graded on a scale of 0 - 3 (0- absent, 1- mild, 2- moderate, 3- severe).
C = the score for pruritus and sleep loss graded on a visual analog scale of 0 to10.The severity is based on the average extent for the last 3 days or nights.

Final formula for calculation of SCORAD is as follows:

- SCORAD = A/5 + 7(B/2) + C
- SCORAD index (0–103) = A⁄5 (20) + 7B⁄2 (0–63) + C (0–20).

The maximum score is 103.

Eczema grading	**Mild**	**Moderate**	**Severe**
SCORAD index	**< 25**	**25–50**	**>50**

The disadvantage of this scoring system is the significant interobserver variation which makes subsequent assessment of the patient by the same observer necessary [(22).]

3- Laboratory investigations:

- All studied subjects were tested for:
- Serum level of Irisin and CRP.

Statistical Analysis

The collected data was revised, coded and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Shapiro-Wilk test was done to test the normality of data distribution. Significant data was considered to be nonparametric

3. Results

Table (1): Comparison of demographic data and nutritional status between moderate and severe AD patients.

Demographic data Variables	**Moderate AD N=12**			**Severe AD N=18**			**p**
Age (years)	**median**	9.5		7.5			0.471
	range	2-24		0.3-36			
Age groups	**Children**	**N, %**	9	75%	16	88.9%	0.364
	Adults	**N, %**	3	25%	2	11.1%	
Gender	**Male**	**N, %**	6	50%	12	66.7%	0.458
	Females	**N, %**	6	50%	6	33.3%	
Nutritional status	**Normal weight**	**N, %**	12	100%	15	83.3%	0.329
	Overweight	**N, %**	0	0%	2	11.1%	
	Obese	**N, %**	0	0%	1	5.6%	

Age is compared using Mann Whitney test; gender and age groups by chi square and nutritional status by Fisher exact test

No significant differences (p>0.05) were found regarding age, sex, nutritional status between moderate and severe AD patients as shown in the table 1

Table (2): Clinical data of studied AD patients.

Variables			**Moderate AD N=12**	**Severe AD N=18**	**Total N=30**	**p**
Age of onset (years)		**mean±SD**	4.4 ±1.2	5.2 ± 1.7	4.8 ± 1.3	0.561
Duration (months)		**mean±SD**	33.3 ±10.1	30.3 ± 9.5	24 ± 10.1	0.654
Positive family history		**N (%)**	4 (33.3%)	1 (5.6%)	5 (16.7%)	0.128
Sites	**Head and neck**	**N (%)**	8 (66.7%)	13 (72.2%)	27 (90%)	0.745
	Upper extremities	**N (%)**	7 (58.3%)	13 (72.2%)	20 (66.7%)	0.461
	Lower extremities	**N (%)**	7 (58.3%)	13 (72.2%)	20 (66.7%)	0.461
	Trunk	**N (%)**	3 (25%)	10 (55.6%)	13 (43.3%)	0.098
Local and systemic manifestations	**Lichenification**	**N (%)**	7 (58.3%)	8 (44.4%)	15 (50%)	0.456
	sleeplessness	**N (%)**	12 (100%)	16 (88.9%)	28 (99.3%)	0.503
	Dryness	**N (%)**	12 (100%)	18 (100%)	30 (100%)	0.702
	Itching	**N (%)**	11 (91.7%)	16 (88.9%)	27 (90%)	0.804
	Scratch marks	**N (%)**	4 (33.3%)	16 (88.9%)	20 (66.7%)	**0.004**
	crustation	**N (%)**	3 (25.0%)	12 (66.7%)	15 (50%)	**0.025**
	Redness	**N (%)**	4 (33.3%)	6 (33.3%)	10 (33.3%)	1
	Oozing	**N (%)**	1 (8.3%)	3 (16.7%)	4 (13.33%)	0.632
	Cough	**N (%)**	3 (25%)	1 (5.6%)	4 (13.33%)	0285
SCORAD		mean±SD	32.4 ± 5	48.4 ±5.3	42 ± 9.5	**<0.001**

T test, S.D, standard deviation

Insignificant differences (p>0.05) were found between patients with moderate and severe AD regarding family history, age of onset, duration and sites of AD (table 2).

On the other hand, scratch marks, crusting and SCORAD were significantly (p > 0.05) high in patients with severe AD compared to those with moderate AD.

Table (3): Comparison of serum Irisin and CRP levels between both studied groups.

Variable		Control N=30		AD N=40		p
Irisin (ng\mL)	**mean±SE**	32.8	±2.5	10.3	±1.6	**<0.001**
	Range	10.6	44	4.1	35.3	
CRP (mg\ L)	**mean±SE**	2.4	±0.2	13.9	±4.2	**0.030**
	Range	0.8	3.6	1.6	98.5	

T- test, SE=Standard Error.

Patients with AD had a significantly lower serum Irisin levels (p> 0.001) (fig.10) and higher CRP levels(p=0.030) when compared to control (table 3).

Table (4): Comparison of Irisin and CRP levels between moderate and severe AD patients.

Variable		Moderate N=12		Severe N=18		p
Irisin	**mean±SE**	16.4	3.2	6.2	0.3	**0.001**
	Range	6.4	35.3	4.1	9.4	
CRP	**mean±SE**	3.7	0.7	20.9	6.5	**0.044**
	Range	1.6	10.4	3.2	98.5	

T- test, SE= Standard Error.

Table 4 shows that severe AD cases showed significantly lower levels of Irisin and higher levels of CRP (p=0.001, 0.044, respectively).

Table (5): AUCs and performance features of Irisin and CRP for discrimination between AD cases and control groups.

	Irisin	CRP
AUC (95% CI)	0.953 (0.903-1)	0.860 (0.757-0.963)
Cut off	27.8	2.9
Sensitivity (%)	93.3	80
Specificity (%)	80	65
PPV (%)	87.5	77.4
NPV (%)	88.8	68.4
Accuracy (%)	88	74

AUC, area under ROC, receiver operating curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Serum Irisin showed excellent AUC (AUC=0.953), while CRP showed good AUC (AUC=0.860). Cut off values and performance features are shown in table (5).

Table (6): AUCs and performance features of serum Irisin and CRP for discrimination between moderate and severe AD patients.

	Irisin	CRP
AUC (95% CI)	0.917 (0.820-1)	0.840 (0.694-0.986)
Cut off	6.7	4.4
Sensitivity (%)	77.8	72.2
Specificity (%)	83.3	83.3
PPV (%)	87.5	86.6
NPV (%)	71.4	66.6
Accuracy (%)	80.0	76.6

AUC, area under ROC, receiver operating curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Irisin showed excellent AUC (AUC=0.917), while CRP showed good AUC (AUC=0.840). Cut off values and performance features are shown in table 6.

Table (7): Correlations of serum Irisin and CRP with other studied parameters in AD group.

Variable	Irisin		CRP	
	r	p	r	p
Age	0.107	0.574	-0.231	0.219
Weight	-0.280	0.139	0.209	0.269
Onset	0.060	0.753	-0.161	0.395
Duration	0.179	0.343	-0.217	0.250
SCORAD	-0.771	**<0.001**	0.736	**<0.001**
CRP	-0.774	**<0.001**		

Spearman correlation analysis, r= correlation coefficient

Table 7 showed that Irisin had a significant negative correlation with SCORAD (r=-0.771, p<0.001) and CRP (r=-0.774, p<0.001). On the other hand, CRP showed significant positive correlation with SCORAD (r=0.736, p<0.001).

Table (8): Regression analysis for prediction of AD susceptibility.

Variable	Univariable				Multivariable			
	P	OR	95% CI		P	OR	95% CI	
Age	0.972	1.001	0.962	1.041				
Gender	0.726	0.880	0.432	1.793				
Nutritional status	0.597	0.749	0.257	2.186				
Positive family history	0.875	1.081	0.412	2.834				
CRP	**0.002**	2.000	1.296	3.089	0.550	1.120	0.772	1.625
Serum Irisin	**0.000**	0.915	0.883	0.949	**0.001**	0.927	0.887	0.969

Logistic regression,OR, odds ratio; CI, confidence interval.

Logistic regression analysis was conducted for prediction of AD susceptibility, using age, gender, nutritional status, family history, CRP and Irisin as covariates. Higher CRP and lower Irisin were significantly associated with risk of AD occurrence in univariable analysis. However, taking significant risk factors into multivariable analysis revealed that only lower Irisin was considered as an independent predictor for atopic dermatitis susceptibility (p> 0.05, table 8).

4. Discussion

This There were 30 patients with moderate and severe Alzheimer's disease (AD) and 20 age and sex matched controls in the research, Between the two categories (moderate and severe), no significant differences were found in age, gender, family history, age at which AD first appeared, duration, or location of the disease. Because local manifestations (such as scratch marks and crusting) and SCORAD index mean scores are the primary ways to distinguish between moderate and severe skin conditions, this isn't unexpected. Earlier research had suggested this to be the case (23; 24; 25). With regard to SCORAD index evaluation in newborns and young children with AD, Rullo et al. (23), evaluated whether two observers could agree on the severity of the condition. They also looked at the inter-observer variance in the score, as well as the variation in factors that form the score. Once they had verified their AD scoring system, they discovered that the SCORAD approach worked very well in detecting and evaluating the progression of AD. There was agreement among Boguniewicz et al. (24), Weidinger et al. (25) on the usefulness of the SCORAD scoring system in determining the severity of Alzheimer's disease

Patients with Alzheimer's disease had much higher CRP levels than those in the study's control group, the researchers found. Compared to individuals with intermediate Alzheimer's, those with severe Alzheimer's had much higher CRP levels.

It is now well accepted that AD includes a significant systemic inflammatory component that is directly connected to skin inflammation generally, which is supported by the present study's finding of higher CRP levels in the disease (3). Studies by Hayes et al. (26) and Sinikumpu et al. (27), who found higher CRP levels in individuals with Alzheimer's disease, validated our results. CRP levels were significantly greater in patients with severe AD compared to those with mild AD. Similarly, Vekaria et al. (28) found CRP to be a reliable predictor of the severity of Alzheimer's disease.

Patients with AD had considerably lower levels of serum Irisin than those in the control group, and those with severe AD had much lower levels of serum Irisin than those with mild AD, according to the results of this research.

This is the first research to look at Irisin levels in Alzheimer's patients, to the best of our knowledge. There is a wide distribution of Irisin throughout the body, including skeletal muscle, cardiac muscle, adipose tissue, the pancreas, the kidney, and the brain (29). Irisin is not just a myokine, but also an adipokine having both auto- and paracrine effects, according to research (30). Obese people had lower levels of serum Irisin than normal-weight patients in this investigation, despite the fact that there was no statistically

significant difference between the two groups. Ali et al. (31) said that obesity increases the risk of developing Alzheimer's disease.

The research of Mustafa & El-Shimi (32) found a correlation between decreased serum Irisin levels in acne vulgaris patients and the severity of the condition. Irisin has also been researched by Bulur et al. (33), who found that serum Irisin levels were considerably lower in patients than in the control group and that PASI scores and serum Irisin levels were significantly positively associated.

Research by Farag et al. (34) indicated that serum resistin levels were considerably lower among individuals with AD than in the healthy control group, shedding light on the link between other adipokines and AD. In addition, Han et al. discovered that adiponectin levels were lower in AD patients (35). Leptin, another adipokine, was examined by Jaworek et al. (36), who discovered that AD was linked to lower levels of leptin.

AD patients had reduced Irisin levels and a negative correlation with SCORAD scores, which suggests an anti-inflammatory effect for the hormone. Serum resistin levels in Alzheimer's disease patients were shown to be lower in both Farag et al. (34) and Jaworek et al. (36) than in the control group. Thus, they hypothesised that resistin's anti-inflammatory properties may have a role in the development of Alzheimer's disease. Resistin serum concentrations were shown to have a substantial negative connection with illness severity and a negative link with leukocytosis, which supported this hypothesis. When compared to the control group, Banihani et al. (37) reported a substantial decrease in resistin in 75 AD patients (children and adults).

According to Han et al. (35), total IgE and adiponectin are negatively associated with illness severity, highlighting the importance of this relationship. Serum adiponectin levels were considerably lower in AD patients compared to healthy controls, with a declining trend seen with increasing severity of eczema.

Adipokines may play a role in the complex signalling networks controlling metabolic skin homeostasis, according to the researchers. Adverse skin homeostasis does not seem to be linked to obesity as previously assumed. Adipomyokine Irisin has been identified as the most likely candidate for its role in eczema severity, which might assist forecast disease flare-ups and design focused treatment strategies for eczema sufferers.

Irisin levels were found to be more reliable than CRP when it came to the diagnosis of Alzheimer's disease and the severity of the disease, as evidenced by a higher AUC (0.953 for Irisin versus 0.86 for CRP) in the differentiation between the control group and AD patients and a higher AUC in the differentiation between moderate and severe AD cases (0.917 compared to 0.84 for CRP). Both, on the other hand, exhibited impressive diagnostic and prognostic efficacy (discrimination power was excellent in CRP and outstanding in Irisin).

There was a strong negative link between the SCORAD scoring system and Irisin, as well as a strong positive correlation with C-reactive protein. Patients with Alzheimer's disease (AD) may be less active because to reduced Irisin levels and a negative association with the SCORAD index score, which has recently been linked to an increase in pain intensity (39). Anti-inflammatory effects on cytokine expression and release might explain some of the higher levels in control (40). In the same way, the positive connection between CRP and SCORAD index scores reflects the previously established inflammatory condition linked with Alzheimer's disease (41).

There were also negative correlations between CRP and Irisin. Only Irisin and CRP exhibited statistical significance in a univariate regression study of the independent variables predicting AD incidence. In multivariable analysis, however, only Irisin levels were shown to be predictors of AD susceptibility when important risk variables were taken into consideration. Irisin is clearly better than CRP in this regard. All of these data support the new adipomyokine, Irisin, as a diagnostic and predictive biomarker for Alzheimer's disease.

Serum levels of CRP and other inflammatory biomarkers, as well as Irisin, have been demonstrated to be altered by muscular tension (42). This research suggests that Irisin levels and C-reactive protein levels are linked. Several research have examined the probable link between Irisin and CRP. Furthermore, according to Hou et al. (43), high-sensitivity CRP was substantially and inversely associated with Irisin levels. Patients with knee osteoarthritis were studied by Mao et al. (44) who found that their blood levels of Irisin were reduced. But another research demonstrated a strong association between Irisin and high-sensitivity CRP levels in the general population (45). No connection was found between Irisin and high-sensitivity CRP in healthy persons in a research by Jameel et al. (46). This discrepancy in findings is mostly due to the fact that most research that have indicated non-correlation or positive association used healthy participants.

5. Conclusion

Both CRP and Irisin may be used to gauge the severity of Alzheimer's disease. Obesity and other variables that reduce Irisin may have a role in the development of Alzheimer's disease.

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