https://doi.org/10.48047/AFJBS.6.Si3.2024.2083-2097

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Exploring the correlation of leptin with lipid profile, liver enzymes, and apolipoprotein E in Iraqi diabetic and non-diabetic patients with rheumatoid arthritis

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Volume 6, Issue Si3, May 2024

Received: 26 April 2024

Accepted: 20 May 2024

doi: 10.48047/AFJBS.6.Si3.2024.2083-2097

Abstract

In this study, leptin hormone levels were measured by using the ELISA technique in serum samples taken from 300 Iraqi adults of both sexes, 100 healthy people as a control group, 100 people with only rheumatoid arthritis (RA), and 100 patients with both RA and type 2 diabetes (DM). Then, the relationship between leptin concentration and blood sugar, lipid profile, liver enzymes (Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP)), and Apolipoprotein E (ApoE) in health, RA, and RA & DM people were investigated. Results show that leptin has an inverse and insignificant relationship with cholesterol, triglyceride, and low-density lipoprotein, while it has a direct and insignificant relationship with high-density lipoprotein. RA & DM patients showed an inverse correlation between leptin and AST. There was no positive or significant correlation for the rest of the enzymes. Regarding the relationship between leptin and liver enzymes, the normal state showed an inverse relationship between leptin and ALT levels, while the rest of the relationships were direct and insignificant. Leptin showed a positive correlation with AST and ALT and a non-significant inverse correlation with ALP in subjects with RA. RA & DM showed an inverse correlation between leptin and AST.

Keywords: Leptin, Rheumatoid arthritis, Type 2 diabetes, Apolipoprotein E, Liver enzyme, Lipid profile.

1. Introduction

Autoimmune diseases are a group of diseases in which the immune system recognizes the body's tissues as foreign and attacks them. Important autoimmune diseases include diabetes and rheumatoid arthritis (RA) [1]. Type 2 diabetes (diabetes mellitus, DM) is caused by insufficient insulin synthesis and function in the pancreas and is characterized by hyperglycemia (high blood glucose levels) [2]. A long-term increase in the concentration of glucose in the blood causes secondary effects such as heart disease, kidney disease, stroke, and blindness [3].

RA is an autoimmune disease that inflames the tissue covering the joints (synovium). A combination of environmental, hormonal, and genetic factors causes inflammation and RA. Its symptoms are fever, fatigue, weight loss, pain, swelling, and joint stiffness. Early diagnosis and treatment can slow down the disease process. However, the process of its appearance and progress varies in different people, and there is no definitive treatment for RA [4].

RA and DM are both chronic inflammatory conditions. These two diseases may exist simultaneously in the same person. While they affect separate parts and tissues of the body, there is a complex relationship between them. About 16% of people with RA have DM, while 47% of people with DMs have RA [5]. Tumor necrosis factors alpha (TNF-α), interleukin-6 (IL-6), and C-reactive proteins (CRP) increase in diabetes and RA. These cytokines disrupt the insulin signaling pathway and aggravate DMs [6].

Leptin is a hormone from the family of cytokines (interleukin) that is coded by the obesity gene and after processing its amino acids are reduced from 176 to 146 [7]. The crystal structure of leptin has four alpha helices connected by turns and loops. Leptins are mostly secreted by white adipose tissue, however brown adipose tissue, placenta, skeletal system, pituitary, bone marrow, and liver are also able to produce leptin [8, 9]. Increasing leptin levels causes cytokine regulation in part of immune responses [10]. Leptin activates T cells in processes leading to inflammation. It also enhances the synthesis of cytokines such as TNF-α and IL-6 by macrophage/monocyte cells. Leptins affect innate and adaptive immunity mod, rate the toxicity of natural killer cells, and increase the proliferation and phagocytosis of monocytes and macrophages. Leptins also increase the immune responses of T helper cells 1 and decrease the immune responses of T helper cells 2, thus enhancing T cell proliferation from the perspective of adaptive immunity [11]. In addition to the mentioned cases, leptin modulates the activity of regulatory T cells and inhibits autoimmunity [12]. Therefore, leptin can be considered a gateway for metabolic health and communication among autoimmune patients. Nowadays, techniques related to the leptin signaling pathway are used to treat autoimmune diseases such as RA [13]. In connection with the effect of leptin on metabolism, leptin inhibits insulin secretion and increases insulin resistance [14]. Therefore, leptin increases lipolysis with the opposite effects of insulin. As a result, triglyceride accumulates in non-fat tissue and causes the pathological condition of lipotoxicity [14, 15]. The greatest accumulation of toxic lipids is in liver cells [15]. There is a close relationship between insulin secretion and fat metabolism with leptin levels. Studies show that long-term exposure to insulin induces leptin secretion [16]. In another study by Pereira et al. [17], it was shown that the rate of fatty acid

production from glucose was decreased for rats exposed to 10 ng/ml leptin (for 6 hours). On the other hand, the flow of triglyceride hydrolysis increased, and the concentration of fatty acid resulting from the lipolysis of triglycerides increased [17].

Considering the importance of blood sugar, lipid profile, liver enzymes as well as apolipoprotein E (ApoE) (in the transport of lipids between different organs and between specific tissues [18]) in RA and DM patients, in this study, the relationship between leptin and these factors in healthy people, patients with RA (non-diabetic), and patients with both RA and DM simultaneously (RA & DM) were examined. The measurement of the desired factors was done mainly using the ELISA method.

2. Methods and materials

This case study was conducted on Iraqi individuals from July 2022 to March 2023. The grouping was listed in order. The total number of participants in the study was 300 individuals, study groups included the following:

Group 1: 100 RA patients without diabetes, Group 2: 100 patients with AR and DM aged 30-70 years from Karama Teaching Hospital, and Al-Zahra Teaching Hospital, Kut, Iraq; and Group 3: 100 Healthy people were categorized as the control group their age (30-60 years).

Sample preparation: Blood samples were initially collected for subjects. Serum separator tubes were allowed to clot for 30 min before centrifugation for 10 min at 1850 × g. The serum was separated and stored at −80 °C for the next steps.

ELISA: Kits for assessing cholesterol, HDL-cholesterol, triglyceride, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and glucose were purchased from Biolabo (Biolabo Co, France). The leptin human ELISA Kit was obtained from Elabscience Co. (USA) and the ApoE human ELISA Kit was obtained from Abcam Co. (UK). ELISA Reader, Human Co. (Germany), was used for the assays.

The measurement was carried out according to the instructions of the kit manufacturer. In the case of glucose, the measuring was the Trinder method. The Leptin kit was based on the sandwich ELISA method. The assay method of peptide profile kits was based on colorimetry, and liver enzyme assay kits were based on enzyme activity.

Statistical analysis: SPSS version 24 analysis program, T-test statistical analysis, was used to express the probability, mean ± standard deviation (SD), Pearson's chi-square, correlation coefficient, and individual ratio to show the importance of polymorphism and related parameters between the analyzed groups.

3. Result and discussion

3.1 Fasting blood sugar (FBS) content

The study results showed no significant difference in the FBS levels between the group with RA as compared with the control group (p-value > 0.01), and there are significant differences in FBS levels between DM patients and the control group (P < 0.01). This indicates that the RA factor has no significant effect on the rise in FBS in healthy people. The results of the study also showed that there are statistically significant differences in the FBS levels among people with RA compared to patients with RA & DM, where the p-value is less than 0.01, and this means that there is a significant difference and a clear effect of the RA factor on rising of FBS in diabetes patients (Table 1). Figure *1*A also shows all the significant and non-significant differences between the study groups.

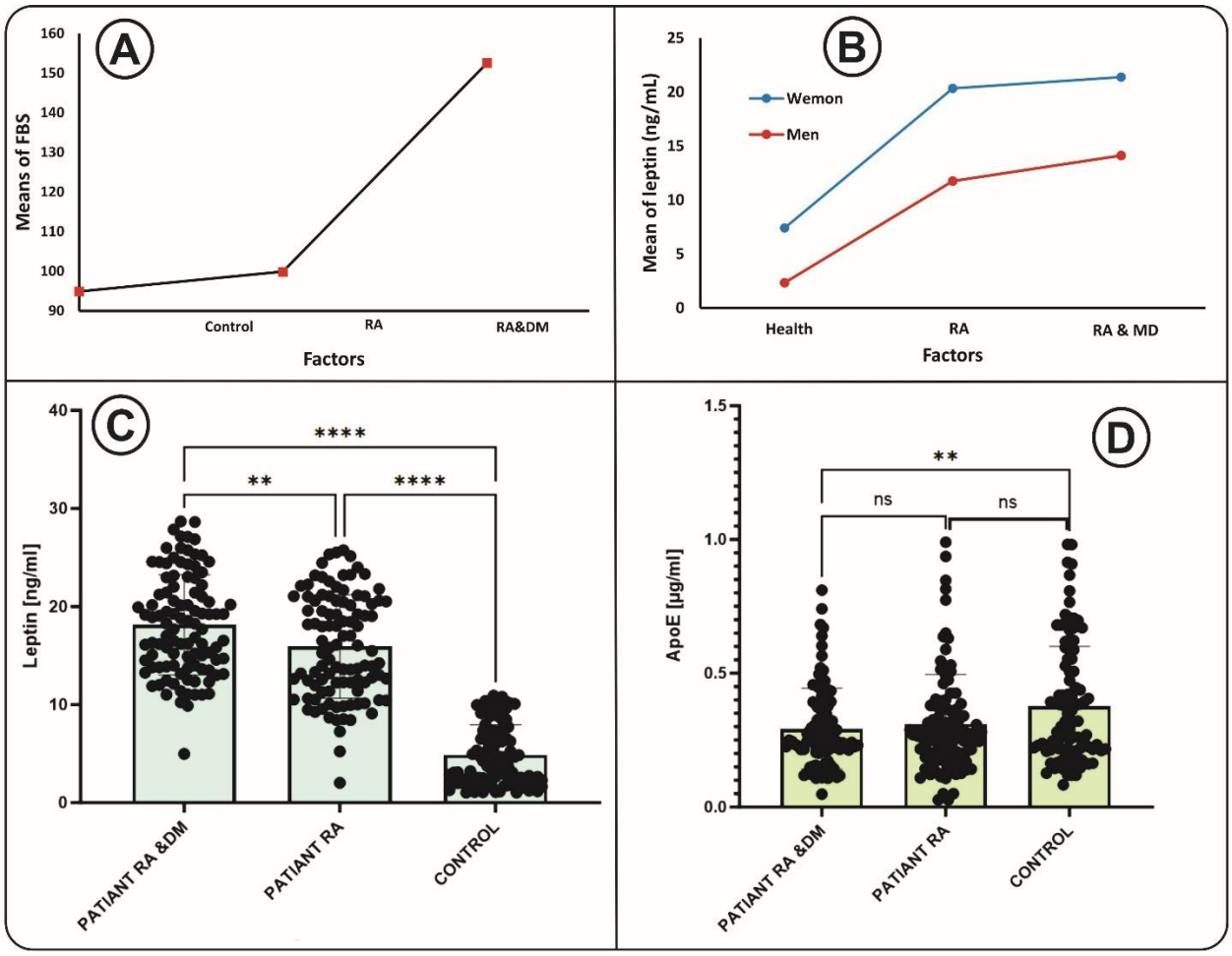

Figure 1. Significance difference between FBS (A) and leptin (B) factors in health, RA and RA & DM groups. Differences in mean serum leptin levels in study groups (C). The differences in Mean+SD serum levels of ApoE among study groups (D). Data were represented as mean ± SD and significant differences indicated by star symbol (ns= non-significant and **, P<0.01 and ****, P<0.0001).

Table 1. FBS of investigated groups.

Cases		Mean Difference	p-value	99% Confidence Interval	
				Lower Bound	Upper Bound
Control	**RA**	4.88000	0.0019	11.5773	1.8173
	DM & RA	57.63000	<0.0001	64.3273	50.9327
RA	**Control**	4.88000	0.0019	1.8173	11.5773
	DM & RA	52.75000	<0.0001	59.4473	46.0527
DM with RA	**Control**	57.63000	<0.0001	50.9327	64.3273
	RA	52.75000	<0.0001	46.0527	59.4473

Chronic, low-grade inflammation is a feature of DM, and it may contribute to the development of more severe inflammatory conditions like RA. Patients with DM usually have high levels of inflammatory mediators such as CRP, IL-6, and TNF-α [19]. DM, insulin resistance, and impaired glucose metabolism are often seen in RA patients [20]. In the current study, there were significant differences among the studied categories regarding the estimation of FBS levels, especially among patients with diabetes and the control group; this is normal. The results of the study also showed that there were no significant differences in FBS levels between patients with RA when compared to the control, perhaps due to the levels of disease in the study groups or the lifestyle followed as well as the type of treatments This may agree with the results of the study conducted by Arias De La Rosa et al. [21], They indicated that the metabolic perturbations associated with RA depend on the level of inflammation and identify adipose tissue inflammation as a primary target leading to insulin resistance and molecular perturbations associated with carbohydrate and lipid homeostasis. The results of this study also do not agree with the findings of Ristić et al. [22], which indicated that rheumatoid arthritis plays an important role in the glucose metabolism disorder. The inflammatory role in the development of diabetes and high glucose levels may play key roles in the severity of rheumatoid arthritis. The results also showed that there are highly significant differences in the level of FBS among people with RA with DM when compared to the control group, as well as comparing them to people with rheumatoid arthritis only (Figure *1*A). Insulin resistance and diabetes mellitus are more likely to occur when systemic inflammation levels are high [23]. Elevated CRP and IL-6 indicators of systemic inflammation were predictive of the development of diabetes mellitus [24]. Another study found that the long-term development of diabetes was linked to inflammatory indicators such as CRP, an increased white cell count, and a lower serum albumin level [25]. The potential role of insulin resistance as a cardiovascular risk factor in patients with inflammatory arthritis was also examined. It was also found that there was an impairment in glucose processing in a sample of RA patients compared to controls.

3.2 Leptin concentration

The study indicated that there are significant differences in leptin concentrations, especially between women and men, and this is normal and may be obvious, but we did not address it statistically. Results also showed a significant difference in leptin concentrations in men and women when comparing the study groups between them, as shown in Table 2. Patients with rheumatoid arthritis may develop diabetes primarily as a result of elevated leptin levels. This implies that leptin affects the promotion of diabetes. Figure *1*B shows all the significant differences between the study groups.

Table 2. Concentration of leptin in Healthy, RA, and RA & DM patients' women and men groups.

Cases		Mean Difference	p-value	99% Confidence Interval	
				Lower Bound	Upper Bound
Women					
Healthy	**RA**	12.92441*	0.0001	14.7525	11.0964
	RA & DM	15.01286*	<0.0001	16.8409	13.1848
RA	**Healthy**	12.92441*	0.0001	11.0964	14.7525
	RA & DM	2.08845*	0.0042	3.9165	0.2604
RA & DM	**Healthy**	15.01286*	<0.0001	13.1848	16.8409
	RA	2.08845*	0.0042	0.2604	3.9165
Men					
Healthy	**RA**	9.39598	<0.0001	10.4871	8.3049
	RA & DM	11.72016*	<0.0001	12.8113	10.6290
RA	**Healthy**	9.39598*	<0.0001	8.3049	10.4871
	RA & DM	2.32418*	0.003	3.4153	1.2331
RA & DM	**Healthy**	11.72016*	<0.0001	10.6290	12.8113
	RA	2.32418*	0.003	1.2331	3.4153

* The mean difference is significant at the 0.01 level.

Figure *1*C indicates a significant increase in the average leptin level in the RA group (16.03 ± 5.227 ng/ml) and in RA & DM patients (18.23±5.007 ng/ml) compared to the healthy control group (4.871 ±3.097 ng/ml), it appears that there is a significant difference when compared to the control group ($P < 0.01$). Also, there was a significant difference when comparing the disease groups among themselves (RA & DM patients and RA patients) ($p < 0.02$). Our study's results align with another study that suggests that TNF-α, IL-1, and IL-6 are the causative causes of RA, although

the precise etiology remains unknown despite several cytokines. This is because infection and inflammation raise leptin levels, which indicates that leptin is a part of the cytokine network that modulates the immune response [26]. The findings of this study also corroborate another study, which found that leptin influences T cell activation, which aids in the cellular immune response and plays an essential role in the process of T cells linked to inflammation. Leptin stimulates monocyte/phagocyte activity and promotes the synthesis of pro-inflammatory cytokines, such as TNF-α and IL-6. In addition, it allows the release of IL-2 and interferon-gamma from T cells with a Th1 phenotype [27].

3.4 ApoE concentration

The results of ApoE concentration in the serum of desired groups are shown in Table 3. These results indicated a non-significant relationship in the concentration of ApoE in the sera of patients with RA and RA & DM when compared among themselves as well as when compared with the control group ($P > 0.01$) such as showed in Figure 1D.

Table 3. ApoE of investigated in healthy, RA, and RA & DM groups.

Cases		Mean Difference	p-value	99% Confidence Interval	
				Lower Bound	Upper Bound
Healthy	**RA**	0.06711	0.035	0.0119	0.1461
	RA & DM	0.08465*	0.005	0.0057	0.1636
RA	**Healthy**	0.06711*	0.035	0.1461	0.0119
	RA & DM	0.01754*	0.791	0.0614	0.0965
RA & DM	**Healthy**	0.08465*	0.005	0.1636	0.0057
	RA	0.01754*	0.791	0.0965	0.0614

* The mean difference is significant at the 0.01 level.

Gao et al. [28], the study indicated that ApoE may play an important role in the development of dyslipidemia in patients with RA, contrary to the results obtained in the present study. The results are consistent with another study conducted by Vgot et al. [29], which indicated no significant relationship between ApoE and RA in patients. Our findings are also consistent with another study in Norwegian rheumatoid arthritis patients, which, investigated the correlation of ApoE with RA [30].

3.5 Leptin and lipid profile

The Pearson correlation coefficient test between leptin levels and blood lipid profile in the study groups is shown in 3.6 Leptin and liver enzymes

The Pearson correlation coefficient test between leptin levels and liver enzymes in the study groups is shown in Table 5. There was no significant correlation found in this study between liver

parameters and leptin levels in the study groups (P > 0.05). Except for the ALT, where the findings demonstrated a strong positive correlation between leptin and ALT in RA patients (Table 5). Nevertheless, the findings also indicated that, in the healthy group, there is a weak negative correlation with ALT and a weak positive correlation with AST and ALP. In RA patients, the results of the study showed that there is a weak direct relationship between leptin, ALT, and AST, and a weak inverse relationship with ALP.

Table *4*. There was no significant correlation between the lipid levels of research groups and leptin levels (P > 0.05). However, there is a negative correlation between leptin levels and lipid content in all studied groups except for HDL, where the relationship was positive and insignificant in people with RA. The results of the study also showed a significant positive relationship in the group of DM patients with RA. Previous studies have indicated that leptin may increase the accumulation of cholesterol esters in foam cells, especially at high glucose concentrations [31]. Leptin, however, could shield macrophages against too much cholesterol when blood sugar levels are normal [32]. The results of our studies are not consistent with another study that reported an inverse relationship between leptin and HDL cholesterol in humans [33].This inverse association may be due to hyperglycemia, which in turn impairs leptin's ability to remove cholesterol from peripheral tissues by lowering HDL and negatively affects local cholesterol balance in diabetics or those suffering from a certain metabolic disorder [34].

3.6 Leptin and liver enzymes

The Pearson correlation coefficient test between leptin levels and liver enzymes in the study groups is shown in Table 5. There was no significant correlation found in this study between liver parameters and leptin levels in the study groups (P > 0.05). Except for the ALT, where the findings demonstrated a strong positive correlation between leptin and ALT in RA patients (Table 5). Nevertheless, the findings also indicated that, in the healthy group, there is a weak negative correlation with ALT and a weak positive correlation with AST and ALP. In RA patients, the results of the study showed that there is a weak direct relationship between leptin, ALT, and AST, and a weak inverse relationship with ALP.

Table 4. Correlation between leptin level and lipid parameters in healthy, RA, and RA& DM groups.

	Leptin	r-value	p-value
Health	**Cholesterol**	−0.135	0.17
	Triglyceride	−0.004	0.96
	HDL	0.046	0.65
	LDL	−0.168	0.09
	VLDL	−0.004	0.96

RA	**Cholesterol**	−0.135	0.17
	Triglyceride	−0.004	0.96
	HDL	0.046	0.65
	LDL	−0.168	0.09
	VLDL	−0.004	0.96
RA & DM	**Cholesterol**	−0.013	0.89
	Triglyceride	−0.003	0.98
	HDL	0.103	0.3
	LDL	−0.014	0.89
	VLDL	−0.003	0.98

These results may reflect the negative impact of RA or its complications, especially with the significant increase in ALT concentration for such a relationship. As for the last group, which included diabetic patients associated with RA, the results of the study showed a weak direct relationship between leptin, ALT, and ALP, and a weak inverse relationship with AST. The disparity in the relationships between the study groups could be a reflection of the detrimental effects of rheumatoid arthritis and the disorders that are linked to it, particularly diabetes

Table 5. Correlation between leptin level and liver parameters in healthy, RA, and RA & DM groups.

	Leptin	**r-value**	**P-value**
Health	**ALT**	−0.153	0.1
	AST	0.174	0.08
	ALP	0.08	0.4
RA	**ALT**	0.39	0.001
	AST	0.1	0.3
	ALP	−0.076	0.4
RA & DM	**ALT**	0.063	0.5
	AST	−0.008	0.9

	ALP	0.083	0.4

The significant positive relationship between leptin and ALT in the second study group, that is, in people with rheumatoid arthritis, may be normal, as a study indicated that ALT is closely related to fat accumulation in the liver [35]. The results of this study are consistent with Valle-Martos et al. work [36], which indicated a direct relationship between leptin and ALT in inflammatory diseases. According to a different study, rheumatoid arthritis medications have been shown to have a significant impact on ALT level alteration and a cycle leading to an increase in leptin levels, which in turn heightens inflammation stimulation and hepatic pathway disturbance [37]. High levels of leptin have been associated with the severity of liver disorders, especially in patients with diabetes [38]. Our findings agree with another study conducted in Iraq, which indicated a non-significant, direct relationship between leptin concentration and ALP in people with DM [39]. These results are also consistent with another study in Iraq, which indicated that there is no direct significant correlation between leptin concentration and AST in people suffering from myocardial infarction, which is considered one of the most important complications of rheumatoid arthritis associated with DM [40].

3.7 Correlation between leptin and ApoE

Figure 2 shows the results of the association between leptin and ApoE. As expected, a non-significant negative correlation between blood ApoE levels and serum leptin levels was seen in the control group ($r= -0.044$, $p=0.6$), and a weak non-significant direct correlation in RA group ($r=-0.07$, $p=0.04$). Whereas in the RA with DM patients ($r = 0.139$, $p = 0.1$) the direct correlation was non-significant.

In the normal state, in the healthy group, there was a weak and non-significant inverse correlation, perhaps due to the natural role of ApoE in transporting lipids, which is often in moderate or low concentrations compared to leptin, which is also concentrated in regulating fat storage and the rate of burning calories in the body. In addition, body weight can play an important role in regulating leptin levels and vice versa. Therefore, perhaps the results of the association in this study can be adopted as a natural result, with an emphasis on focusing studies in the future on such a relationship, while taking into account some relevant biochemical indicators. As for the RA group, we note that there is a weak and non-significant direct correlation, meaning that there is an increase in the level of ApoE and leptin. This increase may be weak in most cases and is not directly related to one another, but it is due to the activity of ApoE in cases of RA as well. The high level of leptin may be due to the ApoE increasing reason as mentioned previously. It is worth noting that there is no report explaining the mechanism of the relationship between ApoE and leptin in RA. In the case of rheumatoid arthritis associated with DM, we note a strength association increased compared to other study groups, especially healthy ones, but it wasn't significant. This is probably due to the mostly separate roles that leptin and ApoE play in disease development. The concentration of ApoE may increase and its function may be doubled in DM in terms of lipid

disorders, as well as increasing ApoE production in the joints in the case of RA [29, 41]. Another study indicated that DM is associated with hyperinsulinemia and insulin resistance compared to the control group and that leptin levels in diabetics are greater than in healthy people [42]. Leptin levels may be significantly correlated with the disease severity of rheumatoid arthritis patients. It has been noted that plasma leptin levels are greater than in healthy controls [43]. In patients with arthritis who did not have joint erosion, serum leptin levels were found to be higher than those in synovial fluid, indicating that leptin consumption in the joints may be involved in protecting against erosions. As a result, leptin prevents bone erosion [44]. Our data can be considered as references for this association in the same study groups, taking into account the weight, as well as the biochemical indicators that give a clearer explanation of such a mechanism.

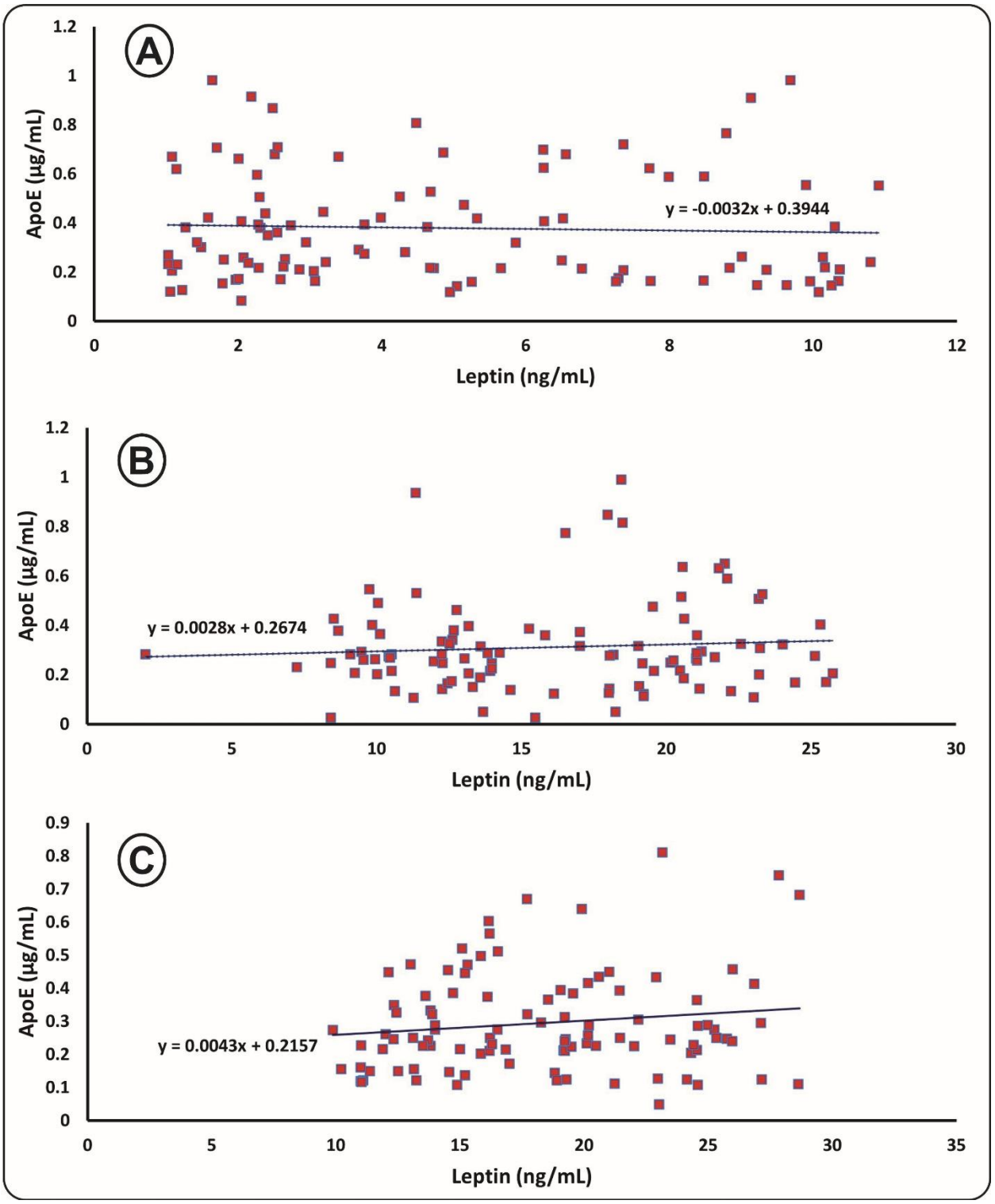

Figure 2. Correlation between leptin and ApoE in control (health) (A), RA (B), and RA & DM (C).

4. Conclusion

In conclusion, fast blood sugar did not make a significant difference (between the control group and RA because blood sugar is naturally high in DM). Leptin plays an important role in the development of RA in both sexes, as there are clear and significant differences between the studied groups. There was no statistically significant difference in ApoE levels in the studied groups compared to the control group. Leptin has an inverse and insignificant relationship with cholesterol, TG, and LDL, while it has a direct and insignificant relationship with HDL. Perhaps this is the most natural and acceptable state in terms of health. RA & DM patients showed an inverse correlation between leptin and AST. There was no positive and significant correlation for the rest of the enzymes. Regarding the relationship between leptin and liver enzymes, the normal state showed an inverse relationship between leptin and ALT levels, while the rest of the relationships were direct and insignificant. Leptin showed a positive correlation with AST and ALT and a non-significant inverse correlation with ALP in subjects with RA. RA & DM showed an inverse correlation between leptin and AST. There was no positive and significant correlation for the rest of the enzymes. The correlation between leptin and ApoE was positive and non-significant in all studied groups.

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