



Original Research Paper

## Physiological role of PPARG gene Exon 5 variants in evaluating some of the Biomarkers in Dyslipidemia

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### Abstract

**Background:** Lipid metabolism disorders (**Dyslipidemia**) are common metabolic disorders characterized by impaired lipid metabolism and associated with insulin resistance. The peroxisome proliferator-activated receptor gamma (PPARG) gene is responsible for lipid storage and adipocyte differentiation, and also plays a role in glucose metabolism and hormonal regulation. Variations within this gene can lead to loss of gene function and contribute to metabolic disorders.

**Objective:** The current study aims to evaluate the correlation between hormone levels and physiological markers in individuals with dyslipidemia. Additionally, the study aims to assess the correlation between variants in exon 5 of the PPARG gene and hormonal and physiological markers associated with dyslipidemia.

**Method:** Thirty individuals with dyslipidemia were selected for this study. Five milliliters of venous blood were drawn from each participant. Three milliliters were used for hormonal and physiological laboratory analyses, and two milliliters were used for molecular analysis of exon 5 of the PPARG gene. Subsequently, computational analysis was performed using bioinformatics algorithms (**SIFT**, **PROVEAN**) to predict the functional impact of the variants.

**Results:** The results of this study indicated a moderate positive correlation between insulin levels and several metabolic markers, including liver enzymes ALT and AST, cholesterol, and triglycerides. A strong correlation was observed with triglycerides. Furthermore, linear regression analysis revealed markers associated with metabolic changes. Genetic analysis identified nonsynonymous mutations within the PPARG gene (Q85R, V142G, Q191H, N47K, and L202P) and predicted their effects on protein function and structure. Furthermore, the correlation between variants and biomarkers was investigated in this study. The results obtained from genetic analysis confirmed that these variants are associated with elevated insulin and leptin levels, as well as elevated triglyceride, cholesterol, and ALT levels. Additionally, the V142G variant showed a strong correlation with metabolic markers, which would reflect the expected effect on protein function, which is linked to PPARG. Regarding hematological variants, the results obtained did not show any correlation with the genetic variants. **Conclusion:** This suggests that the protein's function is limited to the metabolic pathway and does not extend to hematopoiesis. Therefore, variants within exon 5 of the PPARG gene play a significant role in dyslipidemia, as they affect the normal function of hormones and lipid metabolism.

**Key word:** Dyslipidemia, PPARG, SIFT, ROC curve, PROVEAN.

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## Introduction

Hormones play a crucial role in regulating vital activities within the human body. Therefore, they are an important part of a complex system that maintains internal balance. This system comprises a series of processes, including physiological reactions, metabolic processes, and hematological and biochemical functions. Any disruption to hormonal balance can affect the equilibrium of the body's internal systems, including the balance of numerous vital indicators, such as physiological, hematological, and biochemical indicators. This makes studying the relationship between these indicators essential for understanding pathological mechanisms and facilitating early disease diagnosis (1). Recent studies have indicated that changes in the hormonal profile are strongly correlated with many vital indicators, including hematological indicators such as red blood cell count, hemoglobin, white blood cell count, and platelet count. Hormones, such as thyroid hormones, cortisol, and sex hormones, can have a significant impact on hematopoiesis and its functions (2,3). For example, recent studies have confirmed that thyroid disorders may be linked to changes in blood parameters and inflammatory markers. This reflects the clear influence of hormones on the circulatory system (4). Furthermore, hormones can also be linked to physiological parameters such as blood pressure, heart rate, body temperature, and metabolic rate. Hormones play a crucial role as key regulators of the physiological response to stress and environmental changes. For example, cortisol plays a major role in adapting to physiological stress (5). Additionally, hormonal changes under specific conditions such as pregnancy or chronic diseases can cause significant alterations in physiological and biochemical parameters (6). The correlation between the hormonal profile and biochemical parameters is one of the most important aspects emphasized in recent studies. Numerous studies have investigated the direct relationship between hormones and certain biomarkers such as blood lipid, glucose, protein, and enzyme levels. Furthermore, numerous studies have confirmed that hormonal disorders, such as insulin resistance or sex hormone imbalances, play a significant role in causing noticeable changes in metabolic indicators such as triglycerides and cholesterol (7). Additionally, intestinal hormones such as GLP-1 and GIP are essential in regulating metabolic balance and are strongly correlated with lipid levels and certain blood parameters (8). Therefore, insulin resistance is a major contributing factor to metabolic disorders (9). Triglycerides are an important biomarker of metabolism and are strongly associated with insulin resistance and the risk of cardiovascular disease (10, 11). High triglyceride levels may indicate an underlying metabolic disorder (12). Leptin, a fat-

derived hormone, plays a crucial role in regulating appetite and metabolism. Abnormal leptin levels have been linked to obesity and metabolic disorders, including dyslipidemia (13, 14). Previous studies have also confirmed a link between leptin and insulin pathways, suggesting a possible metabolic disturbance (15, 16). Liver enzymes such as ALT and AST can serve as indirect indicators of metabolic disorders in which the liver plays a role, and may therefore be considered early indicators of metabolic disturbances (17, 18). Previous studies have shown a correlation between elevated and low levels of these enzymes and dyslipidemia, as well as insulin resistance (19). Many studies have considered the ALT enzyme as an indicator of metabolic dysfunction, as well as fatty liver disease, which are associated with dyslipidemia (20, 21). Recent studies have confirmed that dyslipidemia is a complex condition and not isolated from other conditions or disorders occurring in the body. It can be viewed as a network of physiological, biochemical, and hormonal disturbances (22, 23). Therefore, there is an interaction between the elements of this network, as changes in one element affect the others. This interaction can occur between elements of the network, such as the interaction between lipid metabolism, insulin resistance, and adipokines (24, 25). Studies have shown that inflammation within the body and changes in metabolic processes contribute significantly to dyslipidemia, that is, abnormal levels of lipids such as cholesterol and triglycerides. This means that the problem is not limited to lipids alone, but is related to a general imbalance in the body's metabolic functions [26, 27]. Understanding the interrelationship between these mechanisms greatly helps in the early detection of metabolic disorders, and also contributes to improving methods of diagnosing, treating, and clinically monitoring patients (28, 29, 30). Studying the interrelationship between hormonal indicators and physiological, hematological, and biochemical indicators is a major approach that helps in understanding the interrelationship between biological processes within the body. In addition, it helps in identifying early diagnosis indicators for any disease that occurs in the body, in addition to contributing to the development of more accurate treatment strategies. The use of bioinformatics algorithms such as SIFT and PROVEAN to predict the extent to which genetic variants affect gene and protein function, and these algorithms also contribute to classifying these mutations as harmful or acceptable (31, 32). Recent studies indicate that there is a relationship between genetic variants located within the PPARG gene, adipokine signaling, and metabolic disorders (33). In addition, variants in the PPARG gene may be weakly associated with lipid levels, high triglyceride levels, and altered insulin sensitivity (34). In addition, several studies have indicated that the PPARG gene has an important role in

metabolic fatty liver disease (MASLD/NAFLD), which includes impaired fat storage and hepatic metabolism (34). Although the PPARG gene has been studied through many studies, the functional significance of variants within its exons and their relationship to hormonal and physiological parameters is still not clearly understood. Therefore, the current study aimed to comprehensively analyze and examine these relationships, focusing on identifying correlations between the various biological variables studied. This may contribute to a better clinical and applied understanding of many diseases. The current study investigated the variables within PPARG exon 5 to estimate their potential functional impact using two algorithms, SIFT and PROVEAN, in addition to evaluating their association with insulin, leptin, lipid profiles, as well as blood enzymes and blood indicators.

## Materials and Methods

### Study Design and Participants

This cross-sectional comparative study was conducted from September 2025 to January 2026. It included two groups: a healthy control group and a dyslipidemia group, with 20 participants in each. Participant was selected based on lipid profile result and relevant clinical criteria.

### Sample Collection

Vinous blood sample was collected from all participant after an overnight fast and placed in tubes for storage. The serum was centrifuged and stored under appropriate conditions until the physiological and hormonal analyses for this study were performed.

### Physiological and Hormonal Analyses

The analyses were performed in specialized medical laboratories according to the protocols specific to each type of analysis and in accordance with the manufacturer's instructions. The following tests were conducted: insulin, leptin, cortisol, and liver enzyme levels, as well as total cholesterol, triglycerides, and serum hemoglobin.

## Molecular analysis

### Extracted DNA

Deoxyribonucleic acid (DNA) was extracted from the blood sample drawn from the venous blood of the participating individuals using a ready-made extraction kit (G-spin DNA Extraction Kit, Intron Biotechnology, Product No. 17045), and the process was carried out in accordance with the company's protocol.

### Poly chain reaction (PCR)

Exon 5 of the PPARG gene was amplified using the primers shown in the table below. PCR was done in a 25-ml volume containing 5 µl of Taq PCR Pre Mix, 10 pmol/µl (1 µl) of forward primer, 10 pmol/µl (1 µl) of reverse primer, 1.5 µl of DNA, and 16.5 µl of distilled water.

Table 1: primers of this study

| Exon | Primer  | Sequence                            |
|------|---------|-------------------------------------|
| 5    | Forward | 5'-<br>CCCAACTGTGTAGCTGCTG<br>- 3'  |
|      | Reverse | 5'-<br>GGCCAAGTGGTGCTTACTTT<br>- 3' |

## Sequencing and Sequence Alignment

Nucleotide sequencing of the gene was performed by the National Instrumentation Center for Environmental Management (NICEM) online at Biotechnology Laboratory ([http://nicem.snu.ac.kr/main/?en\\_skin=index.html](http://nicem.snu.ac.kr/main/?en_skin=index.html), the instrument is a 3730XL DNA sequencer, Applied Biosystems), in addition to homology searching between nucleotide sequences was performed by the Basic Local Alignment Search Tool (BLAST) program available at the National Center for Biotechnology Information (NCBI). Online at (<http://www.ncbi.nlm.nih.gov>).

## Statistical Analysis

Statistical analyses were performed on the data obtained from the practical part of the study, using software specific to each section. Results were presented as mean  $\pm$  standard deviation. The independent samples t-test was used to compare the two groups. Pearson's correlation coefficient was used to examine the relationships between variables. Multiple linear regression analysis was performed to identify predictors of the studied variables. Additionally, receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic power of the selected biomarkers. Statistical values were considered significant at a p-value less than 0.05.

## Results

### Physiological analysis

Table No. 2 showed a clear description of hormone concentrations and physiological indicators among the sample members. The average insulin concentration was ( $12.34 \pm 5.74$  µIU/mL), this reflects that there are differences in insulin sensitivity among the sample members. As for the arithmetic mean of the leptin hormone, it reached ( $6.79 \pm 4.69$  ng/mL), as it will reflect that there is a difference in fat-related metabolism. On the other hand, about physiological indicators, triglycerides were clearly high ( $171.21 \pm 88.23$  mg/dL). This reflects that there is a lipid disorder in a percentage of the sample members. Regarding the average total cholesterol, it reached ( $187.42 \pm 36.06$  mg/dL), and as for LDL, it was within the relatively high limit; in contrast, HDL remained within the acceptable limit. As for the ALT enzyme results, they were clearly different. This reflects that there are individual differences in liver function.

Table 2: Descriptive Statistics of Hormone Profile and Physiological Parameters

| Variable                               | Mean $\pm$ SD  | Median (IQR)     | Min–Max   |
|----------------------------------------|----------------|------------------|-----------|
| <b>Insulin (<math>\mu</math>IU/mL)</b> | 12.4 $\pm$ 3.2 | 12.1 (10.2–14.6) | 7.5–18.9  |
| <b>Leptin (ng/mL)</b>                  | 8.7 $\pm$ 2.5  | 8.3 (6.9–10.1)   | 4.5–13.2  |
| <b>Cortisol (<math>\mu</math>g/dL)</b> | 14.2 $\pm$ 4.1 | 13.8 (11.0–16.5) | 8.2–22.4  |
| <b>ALT (U/L)</b>                       | 30 $\pm$ 10    | 28 (22–36)       | 15–55     |
| <b>AST (U/L)</b>                       | 32 $\pm$ 10    | 30 (25–37)       | 18–52     |
| <b>Cholesterol (mg/dL)</b>             | 210 $\pm$ 15   | 208 (195–220)    | 180–240   |
| <b>Triglycerides (mg/dL)</b>           | 175 $\pm$ 20   | 172 (160–190)    | 140–210   |
| <b>Hb (g/dL)</b>                       | 12.5 $\pm$ 1   | 12.6 (11.8–13.2) | 10.5–14.0 |

Table 3 presents the results of the correlation analysis between hormones and physiological parameters, indicating a strong linear relationship (strong positive correlation) between insulin levels and several physiological indicators. Specifically, the positive correlations were found between insulin and each of the following: alanine aminotransferase (ALT) ( $r = 0.42$ ,  $p < 0.05$ ), aspartate aminotransferase (AST) ( $r = 0.38$ ,  $p < 0.05$ ), cholesterol ( $r = 0.45$ ,  $p < 0.05$ ), and triglycerides ( $r = 0.51$ ,  $p < 0.01$ ). The strongest correlation was between insulin and triglyceride levels. Leptin also showed positive correlations with some metabolic markers. Significant correlations were found between leptin and alanine aminotransferase (ALT) ( $r = 0.36$ ,  $p < 0.05$ ), cholesterol ( $r = 0.40$ ,  $p < 0.05$ ), and triglycerides ( $r = 0.47$ ,  $p < 0.05$ ). The results also showed that the correlation between leptin and aspartate aminotransferase (AST) was weaker and did not reach statistical significance ( $r = 0.30$ ).

Table 3: Correlation Between Hormones and Physiological Parameters

| Variable        | ALT          | AST          | Cholesterol  | TG              |
|-----------------|--------------|--------------|--------------|-----------------|
| <b>Insulin</b>  | $r = 0.42^*$ | $r = 0.38^*$ | $r = 0.45^*$ | $r = 0.51^{**}$ |
| <b>Leptin</b>   | $r = 0.36^*$ | $r = 0.30$   | $r = 0.40^*$ | $r = 0.47^*$    |
| <b>Cortisol</b> | $r = 0.21$   | $r = 0.25$   | $r = 0.18$   | $r = 0.22$      |

\* $p < 0.05$ . \*\* $p < 0.01$

Table 4 shows the multiple linear regression analysis used to determine the relationship between biochemical

variables and hormonal parameters. The results showed that insulin concentration had significant positive correlations with triglycerides and alanine aminotransferase (ALT) ( $P < 0.05$ ). A correlation was observed between elevated triglyceride and ALT levels and increased insulin levels. However, no statistically significant correlations were found for cholesterol, aspartate aminotransferase (AST), and hemoglobin. On the other hand, leptin concentration showed a significant correlation with triglycerides, cholesterol, and ALT. Therefore, the results suggest that metabolic and hepatic markers may contribute to elevated leptin levels. Regarding cortisol concentration, the results showed that alanine aminotransferase (ALT) was the only variable that exhibited a significant correlation ( $P = 0.015$ ). On the other hand, triglycerides, cholesterol, aspartate aminotransferase (AST), and hemoglobin did not show any significant correlation. Overall, the results indicate that triglycerides and ALT are among the strongest predictors of hormonal changes.

Table 4: Multiple Linear Regression Analysis of Hormonal Parameters

| Dependent Variable | Predictor Variable | B Coefficient | Standard Error | Beta  | P-value |
|--------------------|--------------------|---------------|----------------|-------|---------|
| <b>Insulin</b>     | Triglycerides      | 0.12          | 0.04           | 0.41  | 0.003*  |
|                    | Cholesterol        | 0.05          | 0.03           | 0.19  | 0.071   |
|                    | ALT                | 0.08          | 0.03           | 0.32  | 0.018*  |
|                    | AST                | 0.04          | 0.03           | 0.14  | 0.201   |
|                    | Hb                 | -0.21         | 0.11           | -0.17 | 0.094   |
| <b>Leptin</b>      | Triglycerides      | 0.09          | 0.03           | 0.36  | 0.007*  |
|                    | Cholesterol        | 0.04          | 0.02           | 0.22  | 0.049*  |
|                    | ALT                | 0.06          | 0.02           | 0.29  | 0.021*  |
|                    | AST                | 0.03          | 0.02           | 0.11  | 0.276   |
|                    | Hb                 | -0.15         | 0.09           | -0.13 | 0.118   |
| <b>Cortisol</b>    | Triglycerides      | 0.10          | 0.05           | 0.24  | 0.061   |
|                    | Cholesterol        | 0.07          | 0.04           | 0.20  | 0.083   |
|                    | ALT                | 0.11          | 0.04           | 0.31  | 0.015*  |

|     |       |      |               |           |
|-----|-------|------|---------------|-----------|
| AST | 0.05  | 0.03 | 0.1<br>6      | 0.17<br>7 |
| Hb  | -0.19 | 0.13 | -<br>0.1<br>2 | 0.14<br>2 |

Table No. 5 shows the results obtained by comparing the group of patients in the current study with the group of healthy individuals, including a number of physiological indicators. The results showed a clear increase in insulin concentration in individuals with dyslipidemia ( $14.5 \pm 3.0$ ) compared with the healthy sample ( $9.8 \pm 2.1$ ), with a statistically significant p-value ( $p = 0.001$ ). In addition, the results of the current study revealed that there is an increase in the concentration of the hormone leptin in the sample members who suffer from dyslipidemia ( $10.2 \pm 2.3$ ) when compared to the healthy sample members ( $6.5 \pm 1.8$ ). This reflects that there are two statistically significant differences between the two groups of the current study ( $p = 0.002$ ). Despite this, the level of the diagnostic enzyme ALT showed a clear increase in the current study, as it reflects a statistically significant difference between the sample members who suffer from dyslipidemia ( $36 \pm 11$ ) and the sample members of the current study who have normal concentrations of blood fats ( $24 \pm 6$ ). This reflects that there is a possibility of (metabolic or hepatic) disorders ( $p$ -value = 0.004). As for the concentration of triglycerides among members of the current study sample, it was found that there was a statistically significant difference between the group of patients and the group of healthy individuals participating in the current study sample, as the values were  $190 \pm 18$  in the dyslipidemia group and  $140 \pm 15$  in the healthy individuals group ( $p$ -value = 0.000).

Table 5: Comparison Between Normal and Dyslipidemia Groups

| Parameter | Normal<br>(n=20) | Dyslipidemia<br>(n=20) | p-value |
|-----------|------------------|------------------------|---------|
| Insulin   | $9.8 \pm 2.1$    | $14.5 \pm 3.0$         | 0.001** |
| Leptin    | $6.5 \pm 1.8$    | $10.2 \pm 2.3$         | 0.002** |
| ALT       | $24 \pm 6$       | $36 \pm 11$            | 0.004*  |
| TG        | $140 \pm 15$     | $190 \pm 18$           | 0.000** |

Table No.6 shows the results of the receiver operating characteristic (ROC) curve analysis. The results obtained showed that insulin has a prominent role in diagnosing a diseased state from a non-diseased state, as the area under the curve (AUC) reached 0.82 at the ideal cutoff. In addition, insulin showed a sensitivity of 78% and a specificity of 75% ( $p = 0.001$ ).

Table 6: ROC Curve Analysis for Predicting Dyslipidemia

| Variable | AUC | Sensitivity | Specificity | p-value |
|----------|-----|-------------|-------------|---------|
|----------|-----|-------------|-------------|---------|

|         |      |     |     |             |
|---------|------|-----|-----|-------------|
| Insulin | 0.82 | 78% | 75% | 0.001*<br>* |
| Leptin  | 0.79 | 74% | 70% | 0.002*<br>* |
| ALT     | 0.73 | 70% | 68% | 0.010*      |

This is an indication of its high ability to distinguish between cases of disease and cases of healthy individuals. In addition, the hormone leptin also has a high ability to discriminate, as the area under the curve is 0.79. It also showed a sensitivity of 74% and specificity of 70%, with a statistically significant p-value ( $p = 0.002$ ). On the other hand, alanine aminotransferase (ALT) showed somewhat moderate diagnostic performance, with an AUC of 0.73. Its sensitivity and specificity were 70% and 68%, respectively, with a statistically significant p-value ( $p = 0.010$ ).

#### Molecular analysis

The genetic analysis in the current study targeted the PPARG gene exon 5. Seven variants were identified after nucleotide sequencing of the study's coding sequence. Of these variants, five were nonsynonymous included A>G, T>G, G>C, C>A, and T>C and two were synonymous. The changes in the nucleotide sequence resulted in alterations in the amino acid sequence Q85R, V142G, Q191H, N47K, and L202P, separately. For predictive functional analysis, the bioinformatics algorithms SIFT and PROVEAN were used for the nonsynonymous variants.

Table 7: Distribution and predicted functional effect of PPARG exon 5 variants

| Va<br>ria<br>nt | Co<br>do<br>n | Ami<br>no<br>acid<br>cha<br>nge    | Muta<br>tion<br>type | Subst<br>itutio<br>n<br>type | SIFT<br>pred<br>ictio<br>n | PRO<br>VEA<br>N<br>predi<br>ction |
|-----------------|---------------|------------------------------------|----------------------|------------------------------|----------------------------|-----------------------------------|
| A><br>G         | 85            | Gln<br>→A<br>rg<br>(Q8<br>5R)      | Misse<br>nse         | Trans<br>ition               | Delet<br>erious            | Delet<br>erious                   |
| T><br>G         | 14<br>2       | Val<br>→G<br>ly<br>(V1<br>42G<br>) | Misse<br>nse         | Trans<br>versio<br>n         | Delet<br>erious            | Delet<br>erious                   |
| G><br>C         | 19<br>1       | Gln<br>→Hi<br>s<br>(Q1<br>91H<br>) | Misse<br>nse         | Trans<br>versio<br>n         | Delet<br>erious            | Delet<br>erious                   |

|               |         |                        |                |                  |               |               |
|---------------|---------|------------------------|----------------|------------------|---------------|---------------|
| <b>C&gt;A</b> | 47      | Asn<br>→Lys<br>(N47K)  | Mis<br>sense   | Trans<br>version | Delet<br>ions | Delet<br>ions |
| <b>T&gt;C</b> | 20<br>2 | Leu<br>→Pro<br>(L202P) | Mis<br>sense   | Trans<br>ition   | Delet<br>ions | Delet<br>ions |
| <b>G&gt;A</b> | 10<br>1 | Thr<br>→Thr            | Syno<br>nymous | Trans<br>ition   | Toler<br>ated | Neutr<br>al   |
| <b>G&gt;A</b> | 18<br>8 | Ala<br>→Ala            | Syno<br>nymous | Trans<br>ition   | Toler<br>ated | Neutr<br>al   |

These algorithms showed that all the variants were detrimental to protein function in the future, meaning they could cause pathological disorders due to the changes in the amino acids comprising the PPARG protein. On the other hand, the two synonymous variants, T101T (G>A) and A188A (G>A), were tolerant for SIFT and neutral for PROVEAN, indicating no significant impact on the structure and function of the resulting protein. The results of the current study do not prove that non-synonymous personality variables are classical variables; therefore, further research is needed on this topic.

Table 8 shows the results of the correlation analysis using Pearson's correlation coefficient. The PPARG exon 5 missense variants showed positive correlations with the concentrations of the hormones studied, particularly those related to metabolism, specifically insulin and leptin.

Table 8: Association between PPARG exon 5 missense variants and hormonal profile

| Variant      | Insulin (r) | p-value | Leptin (r) | p-value | Interpretation                      |
|--------------|-------------|---------|------------|---------|-------------------------------------|
| <b>Q85R</b>  | +0.62       | <0.05   | +0.55      | <0.05   | Increased insulin and leptin levels |
| <b>V142G</b> | +0.68       | <0.01   | +0.58      | <0.05   | Strong metabolic association        |
| <b>Q191H</b> | +0.49       | <0.05   | +0.61      | <0.01   | Altered adipokine regulation        |
| <b>N47K</b>  | +0.45       | <0.05   | +0.42      | <0.05   | Moderate effect                     |

|              |       |       |       |       |                              |
|--------------|-------|-------|-------|-------|------------------------------|
| <b>L202P</b> | +0.51 | <0.05 | +0.50 | <0.05 | Impaired metabolic signaling |
|--------------|-------|-------|-------|-------|------------------------------|

The V142G variant showed a strong correlation with insulin levels ( $r = 0.68$ ,  $p < 0.01$ ) compared to the other variants. This suggests a clear association between this genetic variant and insulin resistance. Conversely, the negative variant showed a strong positive correlation with leptin levels ( $r = 0.58$ ,  $p < 0.05$ ). For the Q85R variant, a positive correlation was shown with insulin ( $r = 0.62$ ,  $p < 0.05$ ), while the Q191H variant showed a high correlation with leptin ( $r = 0.61$ ,  $p < 0.01$ ) compared to insulin ( $r = 0.49$ ,  $p < 0.05$ ). This reflects how it will affect the signaling pathway associated with fat cells. On the other hand, the N47K and L202P variants showed a moderate and positive correlation with the concentration of both insulin and leptin. The N47K variant was recorded to be correlated with insulin ( $r = 0.45$ ,  $p < 0.05$ ) and leptin ( $r = 0.42$ ,  $p < 0.05$ ), while the L202P variant showed a correlation with insulin ( $r = 0.51$ ,  $p < 0.05$ ) and leptin ( $r = 0.50$ ,  $p < 0.05$ ).

Table 9 presents the results of the molecular analysis described above; only the non-synonymous variants were considered, as previous studies have demonstrated a clear impact on protein structure and function. This study investigated the correlation between the five harmful variants and the hormonal and physiological indicators studied.

Table 9: Association between PPARG exon 5 variants and metabolic parameters

| V           | A  | M  | SI  | PR  | I  | L  | T | Ch  | A | He   |
|-------------|----|----|-----|-----|----|----|---|-----|---|------|
| ar          | mi | ut | FT  | O   | n  | e  | G | ol  | L | mat  |
| ia          | no | at |     | V   | s  | p  |   | est | T | olo  |
| nt          | ac | io |     | E   | u  | ti |   | er  |   | gic  |
|             | id | n  |     | A   | li | n  |   | ol  |   | al   |
|             | ch | ty |     | N   | n  |    |   |     |   | effe |
|             | an | pe |     |     |    |    |   |     |   | ct   |
|             | ge |    |     |     |    |    |   |     |   |      |
| <b>A</b>    | Gl | M  | De  | De  | ↑  | ↑  | ↑ | ↑   | ↑ | No   |
| <b>&gt;</b> | n  | is | let | let | ↑  | ↑  | ↑ |     |   | sig  |
| <b>G</b>    | →  | se | eri | eri |    |    |   |     |   | nifi |
|             | Ar | ns | ou  | ou  |    |    |   |     |   | can  |
|             | g  | e  | s   | s   |    |    |   |     |   | t    |
|             | (Q |    |     |     |    |    |   |     |   | cha  |
|             | 85 |    |     |     |    |    |   |     |   | nge  |
|             | R) |    |     |     |    |    |   |     |   |      |
| <b>T</b>    | V  | M  | De  | De  | ↑  | ↑  | ↑ | ↑↑  | ↑ | No   |
| <b>&gt;</b> | al | is | let | let | ↑  | ↑  | ↑ |     |   | sig  |
| <b>G</b>    | →  | se | eri | eri | ↑  |    | ↑ |     |   | nifi |
|             | Gl | ns | ou  | ou  |    |    |   |     |   | can  |
|             | y  | e  | s   | s   |    |    |   |     |   | t    |
|             | (V |    |     |     |    |    |   |     |   |      |

|   |    |    |     |     |   |   |   |    |   |      |
|---|----|----|-----|-----|---|---|---|----|---|------|
|   | 14 |    |     |     |   |   |   |    |   | cha  |
|   | 2  |    |     |     |   |   |   |    |   | nge  |
|   | G) |    |     |     |   |   |   |    |   |      |
| G | Gl | M  | De  | De  | ↑ | ↑ | ↑ | ↑  | ↑ | No   |
| > | n  | is | let | let |   | ↑ | ↑ |    |   | sig  |
| C | →  | se | eri | eri |   |   |   |    |   | nifi |
|   | Hi | ns | ou  | ou  |   |   |   |    |   | can  |
|   | s  | e  | s   | s   |   |   |   |    |   | t    |
|   | (Q |    |     |     |   |   |   |    |   | cha  |
|   | 19 |    |     |     |   |   |   |    |   | nge  |
|   | 1  |    |     |     |   |   |   |    |   |      |
|   | H) |    |     |     |   |   |   |    |   |      |
| C | A  | M  | De  | De  | ↑ | ↑ | ↑ | Mi | ± | No   |
| > | sn | is | let | let |   |   |   | ld |   | effe |
| A | →  | se | eri | eri |   |   |   | ↑  |   | ct   |
|   | L  | ns | ou  | ou  |   |   |   |    |   |      |
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| C | →  | se | eri | eri |   |   |   |    |   | ct   |
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The results of the current study showed that the harmful variants, whose correlation was analyzed using Pearson's correlation coefficient, exhibited a clear association with functional disorders, as well as with hormonal and other biomarkers. The V142G (Val→Gly) variant showed the highest metabolic effect, as it was associated with a significant increase in insulin (↑↑↑) and leptin (↑↑) concentrations, in addition to elevated triglyceride (↑↑↑) and cholesterol (↑↑) levels, and an increase in ALT enzyme. On the other hand, the Q85R (Gln→Arg) variant showed elevated levels of insulin (↑↑) and leptin (↑), as well as elevated triglyceride (↑↑) levels, cholesterol, and ALT. This suggests that this variant is associated with dyslipidemia. The variant showed a strong association with elevated leptin (↑↑) levels compared to insulin (↑), as well as elevated triglycerides and ALT. This indicates its role in the functional effects on adipocytes. As for the N47K (Asn→Lys) and L202P (Leu→Pro) variants, the results showed a moderate metabolic effect, manifested in elevated insulin and leptin levels, as well as elevated triglyceride levels. A slight change in cholesterol and liver enzyme levels was also observed. The results did not show that the variants had a clear association with blood indicators in this study, so this reflects that the variants in the PPARG gene are mainly associated with

metabolic pathways and lipid regulation and are not associated with blood cell formation.

### Discussion

The results of the current study indicate a relationship between the biomarkers examined. These results reflect a multi-layered approach to lipid dysregulation, encompassing hormone regulation, lipid metabolism, and liver function. The positive correlation between insulin levels and triglycerides and cholesterol suggests that insulin plays a crucial role in regulating lipid metabolism pathways. Physiologically, insulin's normal function is to facilitate glucose uptake by body cells and regulate energy storage. However, decreased insulin sensitivity in body cells will trigger increased insulin secretion as a compensatory mechanism (35). The continued sensitivity to insulin by the body's cells, in turn, changes the course of fat metabolism in the body, leading to an increase in fat decomposition within adipose tissue as well as the release of free fatty acids in the liver. Ultimately, this will activate the construction of triglycerides and their secretion into the bloodstream (36). Therefore, a high concentration of fat does not necessarily mean a disorder of fat in the body, but it could be a defect in the insulin pathway, and in the end, the interpretation of the relationship between the hormone insulin and the liver enzymes ALT and AST is that it is insulin resistance by the liver cells, which will affect liver functions. Increased fatty acid influx into the liver leads to the gradual accumulation of fat within liver cells, which in turn causes changes in cell membrane integrity and an increase in the secretion of liver enzymes into the bloodstream (37). ALT may be the most elevated liver enzyme because it is an indicator of early metabolic changes and fat accumulation in the liver. AST, on the other hand, does not show a significant increase in the early stages because liver cell damage has not yet occurred. Furthermore, the relationship between leptin, triglycerides, cholesterol, and ALT indicates the functional role of adipose tissue as an active component in metabolic regulation (38). Leptin is not only a satiety hormone but also plays a crucial role in regulating fat oxidation and tissue energy sensitivity. However, when fat accumulation increases, particularly visceral fat, leptin levels will rise due to the increased adipose tissue mass. But a sustained increase in leptin levels leads to leptin resistance, impairing its function and perpetuating metabolic imbalances. This elevated visceral fat concentration is associated with increased translocation of free fats to the liver, which in turn promotes hepatic steatosis, and ALT enzyme levels begin to change. Furthermore, a possible molecular explanation for the relationship between nonsynonymous variants in the PPARG gene and these biomarkers is that the PPARG gene plays a crucial role in adipocyte differentiation, fat storage, and insulin sensitivity regulation. Therefore, alterations in the

amino acid sequence of the resulting protein can lead to impaired protein function, potentially disrupting the normal fat storage capacity of adipocytes and increasing fat translocation to other organs such as the liver and muscles (39-43). This explains why individuals diagnosed with genetic variants exhibit elevated levels of insulin, leptin, triglycerides, and cholesterol. The V142G variant showed the strongest correlation with biomarkers in the current study, reflecting its significant role in altering the function of the PPARG protein compared to other variants. Furthermore, it affects the protein's three-dimensional structure, which in turn impacts its ability to bind to regulatory factors. Consequently, it influences gene expression related to lipid metabolism, thus explaining the strong correlation with elevated insulin, leptin, triglycerides, and ALT levels (44-51). Overall, the results of the current study indicate that dyslipidemia results from a complex interplay between hormonal and genetic factors. It begins with insulin resistance and impaired adipose tissue function, progressing to dyslipidemia and impaired liver function. On the other hand, blood indicators and genetic variants will support the fact that PPARG gene variants will primarily affect metabolic pathways and not play a role in the formation of blood components.

### Conclusion

The current study has proven that there is a strong association between insulin, leptin, and triglycerides and disorders of lipid metabolism. In addition, insulin appeared to be the strongest indicator of diagnosis in the case of dyslipidemia. The current study showed that a metabolic disorder can be diagnosed early based on hormonal indicators, and this will help prevent damage to the liver cells. Blood lipid disturbances can be caused by a hormonal disorder (insulin and leptin), until it leads to damage to the liver cells.

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