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# EFFECT OF ISOTRETINOIN ORAL ON ACNE VULGARIS (A REVIEW OF SYSTEMATIC AND METAANALYSIS STUDIES ON ALANINE AMINOTRANSFERASE LEVELS, ASPARTATE AMINOTRANSFERASE, LIPID PROFILE, HOMEOSTATIC MODEL ASSESSMENT FOR INSULIN RESISTANCE, COMPLETE BLOOD COUNT, FASTING BLOOD GLUCOSE)

Dermatology

**Rr Widya Kusumaningsih*** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia. *Corresponding Author

**Retno Indar Widayati** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

**Diah Adriani Malik** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

**Asih Budiastuti** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

**Puguh Riyanto** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

**Muslimin** Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

## ABSTRACT

**Background:** Oral isotretinoin is known to has a large role in the treatment of acne vulgaris, but unfortunately has significant side effects. Observation of laboratory changes during oral isotretinoin intake is important in order to ensure safety. **Methods:** Medline Pubmed, Scopus, ProQuest, Cochrane library, ClinicalTrials.gov, the reference list, conference proceedings, researchers in field of eligible studies were searched. **Result:** 17 studies (1573 patients) were included into meta-analysis. *Mean difference values* (95% CI) increase for triglycerides 25,81 mg/dL, total cholesterol 16,11 mg/dl, Low-Density Lipoprotein cholesterol (LDL) 15,11 mg/dL, Aspartate Aminotransferase (AST) 3,08 U/L, Alanine Aminotransferase (ALT) 1.61 U/L, hemoglobin 0,18 g/dl, fasting glucose 0,55mg/dL. High-Density Lipoprotein cholesterol (HDL) decrease 3,09 mg/dl, White Blood Cell (WBC) decrease 0.23 $x10^3/\mu L$, neutrophils decrease 0,26 $x10^3/\mu L$. The qualitative analysis found that HOMA IR had increase in mean value. **Conclusion:** Longer laboratory evaluation time, can reduce the cost of treatment and discomfort of patients in acne therapy. Acne patient with abnormal baseline values of laboratory parameters should avoid taking oral isotretinoin

## KEYWORDS

isotretinoin, acne treatment, laboratory monitoring

## INTRODUCTION

Acne vulgaris is an inflammatory, chronic, and immune-mediated disease of the pilosebaseous units of the skin. Acne vulgaris affects 9.4% of the general population worldwide. Acne vulgaris occurs in up to 80% of people between the ages of 11 to 30, although most are seen in the teenage period. Acne often occurs in men, however, the prevalence in women increases with age. Male patients are more likely to have severe acne compared to women. [1–3]

Lesions often occur in areas that have dense sebaceous glands, such as the face, chest, shoulders and back. Acne lesions mainly occur on the face, which can have a major negative impact on the quality of life of the patient. Acne can cause psychological illnesses such as, low self-esteem, anxiety and depression among adolescents and adults. [2]

Systemic isotretinoin is the most effective therapy for severe acne and recalcitrant. Isotretinoin has excellent effectiveness as an acne therapy, and can improve overall quality of life. [2,4]

Studies report that isotretinoin may provide a variety of side effects and changes in laboratory values. Isotretinoin has many controversies associated with several side effects, including teratogenic, hyperlipidemia (increased triglycerides), increased Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), pancreatitis, leukopenia, thrombocytopenia, transaminitis, suicide, insulin resistance, inflammatory bowel. Changes in triglyceride levels, complete blood count values (hematogram), liver function (ALT, AST) and insulin resistance (HOMA-IR) that can be assessed through the patient's serum. High triglyceride levels will progress to pancreatitis, laboratory changes in ALT and AST indicate the function of impaired hepar. These parameters may be related to metabolic syndrome in the future. [2,4–6]

Studies shown about the effects of isotretinoin on laboratory parameters such as liver function tests, lipid profiles and hemograms had various results. Overall, guidelines for laboratory monitoring during isotretinoin therapy were limited by differences in sample number, frequency of testing, tests used in some studies. There is much debate as to whether hematological parameters should be continuously monitored during isotretinoin treatment. Consensus on the frequency of monitoring complete blood counts during isotretinoin therapy has not existed to date. [2]

The purpose of this systematic review and meta-analysis is to combine data throughout published studies for develop estimates of laboratory changes during isotretinoin therapy for acne. We hope to provide information about safety, potential adverse effects and how to manage them, as well as laboratory monitoring to help practitioners optimize the use of oral isotretinoin in treating acne patients, and can be used as a guidance for clinicians in evaluating and making clinical decisions during the use of isotretinoin therapy.

## METHODS

### LITERATURE SEARCH

The following databases were searched until the time of data analysis: Medline Pubmed, Scopus, ProQuest, Cochrane library, ClinicalTrials.gov. The reference list, conference proceedings, researchers in the field of eligible studies were searched to identify additional studies. The following Mesh terms were used for searching: (1) isotretinoin; (2) acne treatment; (3) laboratory monitoring. A literature search was performed by three reviewers independently using PRISMA flow diagram 2009. Differences in opinion were resolved between all reviewers to reach consensus.

### INCLUSION CRITERIA WERE:

clinical trials/publication from 2010 until 2020, participants 12-45 years old, acne vulgaris patients who get isotretinoin therapy, dose 0.2-1 mg /kg day at least 4 weeks. Patients with malignancy and systemic diseases such as liver, kidney and hematological disorders were not involved in the study. Studies were excluded if they: were written neither in Indonesian nor English, were case report, serial case, letter, literature review.

### Data extraction

Data extraction was performed independently by three reviewers. Information included study therapeutic interventions (duration of

treatment and isotretinoin dose), characteristics (sample size, design, country, and duration of therapy), and patient characteristics (sex and age). Laboratory tests included the hepatic panel (AST, ALT), lipid panel (TG, total cholesterol, HDL-C, and LDL-C), fasting blood glucose, HOMA IR, and complete blood cell count. The timing of laboratory monitoring during isotretinoin therapy (at week 4, week 12, week 16, week 24) was recorded. The mean (SD) of the laboratory result and the proportion of patients with abnormal results were recorded.

### Data synthesis

Meta-analysis difference in weighted mean was conducted using Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.Where data was not available to enable pooling, a descriptive synthesis was performe.

## RESULTS

Initial database searches identified 137 non duplicate records. 117 were excluded during the abstract/title and the full-text review. Seventeen studies were included in this review. Figure 1 gives details of the study selection process.

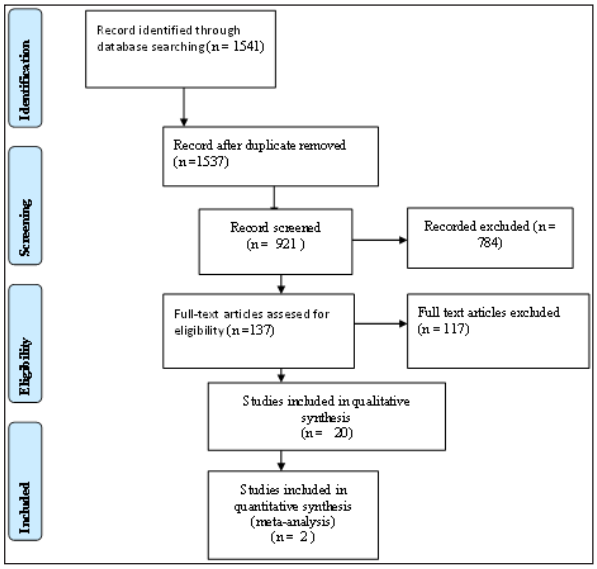


**Figure 1.PRISMA flow diagram**

### Study Characteristics

**The characteristics of included studies are given in Table 1.**

1. Sarac et al 2020. Study conducted on 114 patients, using isotretinoin 0.2-0.5 mg / kg day, at the age of 17-44 years. Examination is performed on the *values of total cholesterol, triglyceride,* aspartate aminotransferase (AST), alanine aminotransferase (ALT), *urea, creatinine, creatinine kinase, uric acid, thrombocyte (Plt) and leucocyte (WBC).* The results of the comparison of baseline and values in the fourth month of treatment showed that levels of *AST, creatinine kinase, cholesterol, triglyceride and thrombocyte* had very significant differences ($p<.001$, $p<0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.02$). The values *of uric acid,* creatinine, ALT and WBC showed statistically insignificant differences ($p>0.05$). [2]
2. Gencoglan 2017. Prospective cohort study in 118 patients, using isotretinoin doses of 0.5–1.0 mg/kg/day to a cumulative dose of 120 mg/kg at ages 15-45 years. Researchers assessed *Platelet, PCT, WBC neutrophil, MCV, HCT,* and *CBC.* The results obtained that platelet and PCT values increased in the first month of treatment and then decreased to baseline. The value *of White blood cells,* neutrophils decreased in the first month, then increased to *baseline* in the second month, and was found to decrease again at the end of treatment. *Mean corpuscle volume* was found to increase at the end of treatment. Other parameters in the CBC show no statistically significant differences. [7]
3. Seckin 2015. Retrospective cohort studies were conducted on 112 patients, using isotretinoin doses of 0.5–1 mg/kg at ages 16-45 years. The study included platelet density, mean platelet volume, neutrophil lymphocyte rate, platelet lymphocyte rate, and red-blood-cell distribution width level. The results obtained significant increase in platelet density, and hemoglobin. Significantly decrease was found in red-blood-cell distribution width, while there was no significant difference in platelet volume, neutrophil lymphocyte rate, platelet lymphocyte rate, and white blood cell count. [8]
4. Kutlu 2019. Prospective cohort studies in 120 patients, using isotretinoin doses of 0.5–1 mg/kg over 12 years old. Examination is performed on the mean platelet volume, plateletcrit (PTC), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), MHR and serum biochemistry, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), urea, creatinine. Results showed mean platelet value, NLR, and PLR decreased statistically significantly after therapy. MHR increases significantly 3 months after ISO treatment. [9]
5. Onder 2020. Prospective cohort studies in 116 patients, using isotretinoin doses of 0.5–1 mg/kg at 16-45 years. Examination is performed on white blood cell (WBC), neutrophils, lymphocytes, monocytes, platelets, mean platelet volume (MPV), platelets, plateletcrites, platelet distribution width (PDW), neutrophilocyte lymph ratio (NLR), platelet lymphocyte ratio (PLR), total cholesterol, LDL cholesterol, triglyceride, HDL cholesterol and MHR. MPV and MHR value improved significantly after 3 months of treatment (p 0.05). There was a significant decrease in the number of neutrophils (p 0.5). Total cholesterol, LDL cholesterol and triglyceride levels increased significantly after three months of treatment ($p<0.05$). [10]
6. Tamer 2019. Retrospective cohort study in 70 patients, using isotretinoin dose of 0.5 mg/kg at 18-37 years. Examination is performed on serum total cholesterol, HDL, LDL, triglyceride, mean corpuscular hemoglobin levels, and platelet/lymphocyte ratio. The results obtained in the form of serum total cholesterol, HDL, LDL, triglyceride, mean corpuscular hemoglobin, and platelet/lymphocyte ratio increased. White blood cell count and mean platelet volume ($p = 0.036$) decrease after isotretinoin treatment. [1]
7. Ahmad 2015. The *Randomized trial* in 58 patients with acne vulgaris, in which patients were inserted and randomized into group I (26 patients) who received a dose once daily, and group II (32 patients) who received twice the daily dose of oral isotretinoin. Examination is performed on serum *cholesterol, triglycerides, Alanine Aminotransferase* (ALT), and *Aspartate Aminotransferase* (AST). Results obtained on the both regimen led to a mild increase in serum cholesterol, *Alanine transaminase* (ALT), and *Aspartat aminotransferase* (AST). The increase in triglycerides had more pronounced especially at twice-daily doses. [11]
8. Yaldiz 2020. Retrospective cohort study in 30 patients, using isotretinoin dose of 0.5 mg/ kg at the age of 18-37 years. Examinations are performed on Distortion Product Otoacoustic Emissions (DPOAEs) and pure tone audiometrytests. Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total cholesterol, triglycerides, High Density Lipoproteins (HDL) and Low-Density Lipoproteins (LDL) cholesterol. The results found that there was a significant increase in total blood cholesterol, triglyceride and LDL levels. HDL values had decreased significantly. [12]
9. Ataseven 2014. A retrospective cohort in 110 patients who received isotretinoin doses of 0.5–1 mg/kg at ages 16-39. The examination is performed on the *Complete blood count.* Platelet *counts* and the mean *platelet volume* decreased significantly after treatment. Hemoglobin, hematocrit, and white blood cell count are not significant differences. [13]
10. Bugdayci 2016. A retrospective cohort in 102 patients received doses of isotretinoin 30 mg/day at ages 15-37. Evaluations were performed on TC, TG, AST, and ALT. The results were interpreted with RCV (Reference *Change* Value), after comparing the first and second doses based on RCV. TC, TG, AST and ALT increased by 12%, 20%, 14% and 12% of patients, respectively. When the first dose was compared to the last dose, the increases were 20%, 29%, 22% and 18% respectively interpreted as significant changes. [14]
11. Ertugrul 2010. Cohort studies in 48 patients used isotretinoin doses of 0.5– 0.75 mg/kg, which were then adjusted to 0.88 mg/ kg/ day at ages 18-38 years. Examination of insulin, C peptide, fasting blood glucose, aspartate and alanine aminotransferases (AST, ALT), *total cholesterol* (TC), *triglyceride, high-density lipoprotein cholesterol* (HDL-C), *low-density lipoprotein* (LDL-C) and very *low-density lipoprotein* cholesterol. AST, ALT, TC,

LDL-C and triglyceride levels significantly increased (P <.01, < 0.05, < 0.01, < 0.05 and < 0.01) but there were no significant changes in fasting blood glucose, insulin, C-peptide, HOMA-IR. [15]

12. Saklamaz 2016. Retrospective cohort studies in 21 patients used isotretinoin doses of 0.5–0.8 mg / kg, at ages 18-34 years. Examination on Blood tests for lipid profile, fasting glucose, liver enzymes, OPN, HOMA-IR, hs-CRP and CIMT. Therapy increases lipid levels, CIMT (0.60-0.74 mm; p 0.001). HOMA-IR (0.91-1.87; p =0.70), OPN (4.32-5.44 ng/ml; p =0.27), hs-CRP (0.08-0.09 mg/dl; p=0.88) did not increase significantly. [16]
13. Ozkol 2014. Retrospective cohort studies in 35 patients who received isotretinoin doses of 0.5– 0.8 mg/kg, at ages 18-34 years. Examination in the form of PON1 activity, Total Oxidant Status (TOS), Total Antioxidant Capacity (TAC), Oxidative Stress Index (OSI) and routine biochemical parameters. The results were PON1 decreased dramatically (p<001), TOS levels and OSI values increased (p<001 and p<001; significant increases were observed in lactate dehydrogenase and gamma glutamyl transpeptidase, total cholesterol levels, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, triglycerides, low density lipoprotein cholesterol/high density lipoprotein cholesterol ratio (p<0.05, p<001, p<001, p<001, p<001, p<001 and p<001) while marked declines were seen in high density lipoprotein cholesterol (p<0.01). [17]
14. Soyuduru G 2019. Case control study, 29 acne patients compared with 29 normal patients using isotretinoin doses of 0.5mg/kg, at the age of over 18 years. Body Mass Index (BMI) and Body Fat Mass (BFM) examinations, lipids, adiponectin, leptin, resistin, retinol binding protein-4 (RBP4), and insulin levels, and insulin resistance were assessed by HOMA-IR index. Fifth month post isotretinoin therapy, a higher HOMA-IR value was found (P = 0.028). [18]
15. Cemil BC 2016. Cohort studies in 32 patients used isotretinoin doses of 0.5– 0.6 mg/kg, at ages 16-25. Examination is performed on BMI, adiponectin, leptin, ghrelin serum. The results of BMI score did not differ significantly. In addition, serum adiponektin and leptin levels increased significantly following isotretinoin therapy. Serum ghrelin levels were no different. [19]
16. Cetinkaya 2019. The cohort study was conducted on 172 people, for 3 months and 6 months. Dose 0.5 mg–1 mg/kg. Examination of triglycerides, total cholesterol, LDL cholesterol, AST, and ALT. The results of these parameters were significantly higher in the 3rd month, and significantly higher in the sixth month of treatment than those in the 3rd month. HDL cholesterol is lower in the sixth month of treatment than it is in the third month of treatment. [20]
17. Karadag 2010 The cohort study in 47 people for 3 months. Doses of 0.5– 0.88 mg/kg. Examination on GF-1 and IGFBP3 levels, GH levels, Aspartate Aminotransferase, total cholesterol, Low-Density Lipoprotein Cholesterol, triglycerides and low-density lipoprotein cholesterol high-density lipoprotein cholesterol ratio. The results of GF-1 and IGFBP3 values decreased significantly (P < 0.01), GH values were unchanged. Aspartate aminotransferase, total cholesterol, low-density lipoprotein cholesterol, triglycerides and Low-Density Lipoprotein Cholesterol /High-Density Lipoprotein Cholesterol Ratio (P < 0.0001) significantly increased, High-Density Lipoprotein Cholesterol Levels decreased significantly (P < 0.0001). [21]

### Risk of Bias in included studies

Risk of bias from 17 studies included in the meta-analysis was performed using The Risk Of Bias In Non-randomized Studies–of Interventions (ROBINS-I) formerly called A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) include bias due to confounding, bias in selection of participants into the study,bias in classification of interventions, bias due to deviations from intended intervention,bias due to missing data,bias in measurement of outcomes,bias in selection of the reported result. [22]

## RESULT

### Lipid Panel

### Triglycerides

The difference in mean values of triglycerides between baseline and post therapy (15.66 weeks) is 25.81 mg/dL (95%CI, 19.87 – 31.74 mg/dL). Z=8.52, P<0.00001, represents a significant increase. The National Institutes of Health Clinical Center's high risk triglyceride value is 200 mg/dL. References based on The Common Terminology Criteria for Adverse Events show a grade 1 value of 150 mg/dL - 300 mg/dL, at grade 2 of 300 mg/dL - 500 mg/dL.

### Total Cholesterol

The mean difference value of total cholesterol between baseline and post therapy (15.71 weeks) is 16.11 mg/dL (95%CI, 13.04 – 19.18 mg/dL). Z =10.28, P<0.00001 represents a significant increase. Reference values from *The National Institutes of Health Clinical Center* on high-risk total cholesterol are 240 mg/dL. References based on *The Common Terminology Criteria for Adverse*

### Low-Density Lipoprotein Cholesterol

The mean difference of LDL value between baseline and after therapy (14,8 weeks) is 15.11 mg/dL (95% CI, 11.36-18.85 mg/dL). Z = 7.91, p = <0.00001 is a significant increase. Reference values from *The National Institutes of Health Clinical Center* on high-risk LDL are 160 mg/dL.

**Table 1. Characteristics of included studies**

| No. | Researchers and Years of Publication | Country | samples | Age | Duration | Research Design | Parameters studied |
|---|---|---|---|---|---|---|---|
| 1 | Sarac, 2019 | Turki | 114 | 17-44 (23,4 ± 6,4) | 4 months | *prospective cohort* | Total cholesterol, Triglycerides, AST, ALT, urea, creatinine, creatinin kinase, uric acid, Platelets, leukocyte |
| 2 | Gencoglan, 2017 | Turki | 118 | 15-45(21.19± 4.33) | 2 months | *prospective cohort* | PLT, PCT, WBC, NEUT, MCV |
| 3 | Seckin, 2015 | Turki | 112 | 22.81± 5.59 | 3 months | *prospective cohort* | Hb, WBC, PLT, MPV, NLR, PLR, RDW |
| 4 | Kutlu, 2019 | Turki | 89 | 18,84 ± 3,8 | 3 months | *prospective cohort* | HB, WBC, PLT, MPV, NLR, PLR, RDW |
| 5 | Onder, 2020 | Turki | 116 | 22.6 ± 4.8 | 3 months | *prospective cohort* | WBC, NEUT, Lymphocytes, Monocytes, platelet, MPV, plateletcrit, PDW, NLR, PLR, total cholesterol, LDL, triglicerides, HDL, MHR |
| 6 | Tamer, 2019 | Turki | 70 | 23.03 ± 4.35 | 3 months | *Retrospective Cohort* | lymphocytes, monocytes, neutrophils. Eosinophils, basophils, total cholesterol, HDL, LDL, Triglycerides, WBC, MVH, MPV, absolute count of limfosit, PLT/L |
| 7 | Ahmad, 2015 | Turki | 58 | 22.12 ± 7.05 | 3 months | Cohort | cholesterol, Triglycerides, ALT, AST |
| 8 | Yaldiz, 2018 | Turki | 30 | 20,5 ±2.7 | 6 months | *Retrospective cohort* | ALT, AST, total cholesterol, triglycerides, HDL, LDL |
| 9 | Ataseven, 2014 | Turki | 110 | 20.73± 5.6 | 3 months | *Retrospective Cohort* | platelet, MPV, Hb, Ht, WBC |
| 10 | Bugdayci, 2016 | Turki | 102 | (15-37) 21.22 ±2.49 | 6 months | *Retrospective cohort* | TC, TG, AST, ALT |
| 11 | Ertugrul, 2010 | Turki | 48 | 18-38 (22) | 3 months | *Cohort* | ALT, AST, TC, LDL-C, Trigliserid, VLDL-C |
| 12 | Saklamaz, 2016 | Turki | 21 | 23.0 ±4.1 | 4 months | *retrospective cohort* | GDP, fasting insulin, HOMA-IR, SGOT, Total cholesterol, Trigliserida, LDL, HDL, Osteopontin, hs CRP,CIMT |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | Ozkol, 2014 | Turki | 35 | (18-30) 21.33 ±3.36 | 3 months | *retrospective cohort* | GDP, BUN, Kreatinin, ALT, AST, LDH, GGT, CK, albumin, Total kolesterol, trigliserida, LDL, HDL, VLDL, LDL/HDL |
| 14 | Soyuduru, 2018 | Turki | 29 | 20.5 ± 1.9 (stud7) 21.4 ±2.5 (control) | 5 months | *case control* | Kolesterol total, LDL, HDL, trigliserida, HOMA, leptin, adiponectin, resistin, RBP4 |
| 15. | Cemil, 2016 | Turki | 32 | 18.9 ± 2.57 | 3 months | *Cohort* | Total cholesterol, trigliserida, LDL, HDL, BMI, adiponektin, |
| 16 | Cetinkaya 2019 | Turki | 172 | 22.2±5.6 | 3 months 6 months | *Cohort* | triglyceride, total cholesterol, LDL cholesterol, AST, and ALT |
| 17 | Karadag 2010 | Turki | 47 | 21.5±5.1 | 3 months | *Cohort* | GF-1 and IGFBP3 levels, GH levels, aspartate aminotransferase, total cholesterol, low-density lipoprotein cholesterol, triglycerides and low-density lipoprotein cholesterol high-density lipoprotein cholesterol ratio |

**High-Density Lipoprotein Cholesterol**

The mean difference of HDL between baseline and post therapy (14.8 weeks) is 3.09 mg/dL (95%CI, -4.71 to -1.48 mg/dL). Z= 3.76, p =0.0002, which is a significant decrease. The reference value of *The National Institutes of Health Clinical Center* on high-risk HDL is 40 mg/dL.

**Aspartate Aminotransferase (AST)**

The mean difference value of AST between baseline and post therapy (17 weeks) is 3.08 U/L (95%CI, 2.04 to 4.13 U/L). Z=5.80. P= 0.00001, which is a significant increase. References based on *The Common Terminology Criteria for Adverse Events* in AST show a grade II value of 108 U/L.

**Alanine Aminotransferase (ALT)**

The ALT mean difference value between baseline and post therapy (17 weeks) is 1.61 U/L (95%CI, -0.07 to 3.03 U/L). Z = 1.87, p = 0.06 which is not significant increase. References based on *The Common Terminology Criteria for Adverse Events* on ALT indicate a grade II value of 111 U/L.

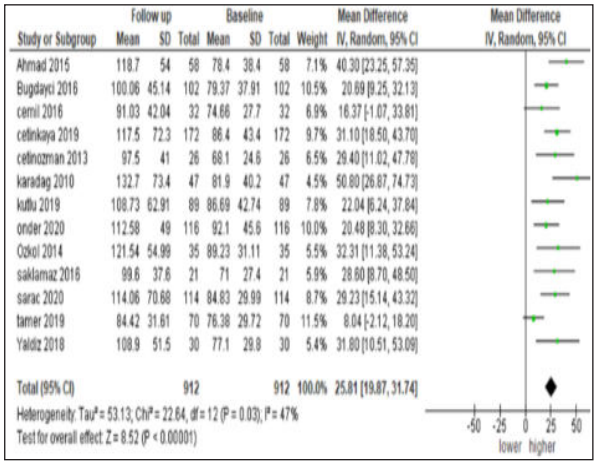


**Table 2. Forest plot of Triglycerides**

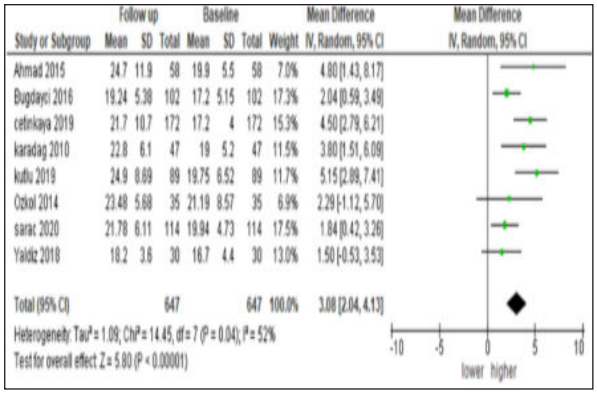


**Table 3. Forest plot of Total Cholesterol**

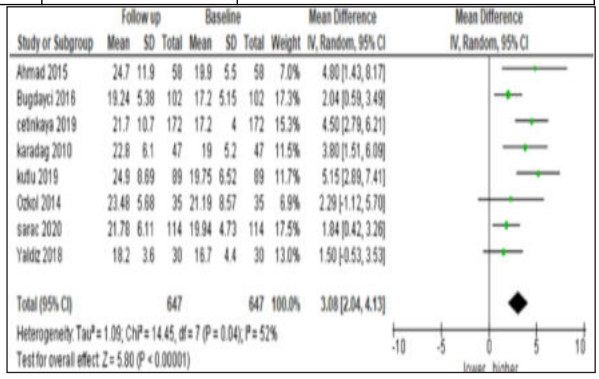


**Table 4. Forest plot of Low-Density Lipoprotein Cholesterol**

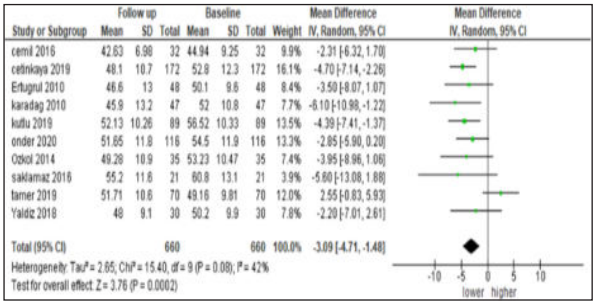


**Table 5. Forest plot of High-Density Lipoprotein Cholesterol**

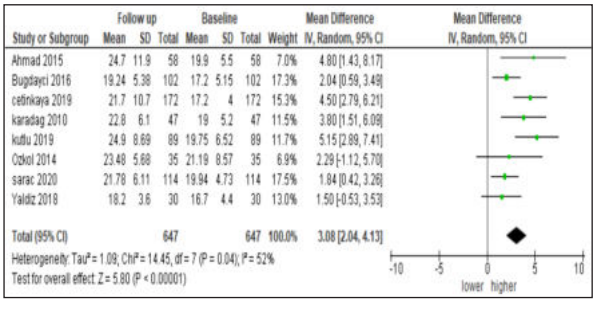


**Table 6. Forest plot of Aspartate Aminotransferase**

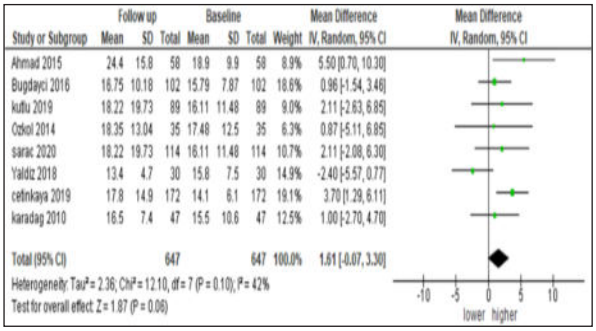


**Table 7. Forest plot of Alanine Aminotransferase**

**Complete Blood Cell Count**

**Hemoglobin**

The mean difference value of Hb between baseline and post therapy (12 weeks) is 0.18 g/dL (95% CI, -0.07 to 0.42 g/dL). Z=1.40, P=0.16 which was an increase, but not significant. References based on *The Common Terminology Criteria for Adverse Events* on Hb indicate a grade II value when it is less than 10 to 8 g/dl /$mm^3$

**WBC**

The mean difference of WBC between baseline and post therapy (mean12 weeks) is 0.23 x103 /µL (95%CI, -0.42 to - 0.04x103/µL). Z = 2.38, p = 0.02 which was a significant decrease. References based on The Common Terminology Criteria for Adverse Events on leukocytes indicate a grade III value when >100,000

**Platelet**

The mean difference value of PLT between baseline and post therapy (11.2 weeks) is 1.85 x103/µL (95%CI, -6.21 to 9.91 x103/µL) Z=0.45, P= 0.65 is an insignificant increase. Normal platelet values 150-400 x103 /µL.

**Monocytes**

The mean difference value of monocytes between baseline and post therapy (11 weeks) was 0.01 $x10^3$/µL(95%CI, -0.01 to 0.03 x10 3/µL). Z=1, P=0.32 were insignificant increases. The normal value of the absolute monocyte count is 0.1 – 0.9 x $x10^3$/µL.

**Basophils**

The mean difference of basophils between baseline and post therapy (10.6 weeks) is 0.00 $x10^3$/µL(95%CI, -0.02 to 0.01 $x10^3$/µL). Z = 0.25, P = 0.8 which was an insignificant decrease. Normal value of absolute basophil count 0-0.1$x10^3$/µL.

**Eosinophil**

The eosinophil's mean difference value between baseline and post therapy (10.6 weeks) is 0.00$x10^3$/µL(95% CI, -0.01 to 0.02 x103/µL). Z= 0.19, P =0.85, insignificant increase. The normal value of the eosinophil absolute count is 0–0.7 $x10^3$/µL.

**MPV**

The mean difference value of MPV between baseline and post therapy (11.3 weeks) is 0.09 fL (95%CI, -0.41 to 0.22 fL). Z=0.58, P= 0.56 was an insignificant decrease. Normal MPV value of 4-11 fL.

**Lyphocytes**

The mean difference of lymphocytes between baseline and post therapy (11 weeks) was 0.01$x10^3$/µL (95%CI, -0.20 to 0.21 $x10^3$/µL). Z=0.05, P=0.96 were insignificant increases. The normal value of absolute lymphocyte count 0.8 - 4 $x10^3$ /µL.

**Neutrophile**

The neutrophile mean difference value between baseline and period after therapy (11 weeks) is -0.26$x10^3$/µL (95%CI, -0.48 to -0.04 $x10^3$/µL). Z = 2.29, P = 0.02 is a significant decrease. The normal netrophile absolute count value is 2-7 $x10^3$/µL

**Fasting glucose**

The mean difference fasting glucose between baseline and the period after therapy (13 weeks) is 0.55 mg/dL (95%CI, -1.47 to 2.56mg/dL) Z = 0.53, p = 0.60 is an insignificant increase. Normal values ≥ 7 years: 70 - 100 mg/dL. Normal values ≥ 7 years old: 70 - 100 mg/dL.

**HOMA IR**

All studies show increased in mean values. The changes are insignificant, except for the Soyoduru study. Normal value <4. Studies cannot be included in meta-analysis study because two studies do not have standard deviation values. Based on the studies collected, all studies show improvements but within normal limits.

## DISCUSSION

This study was a meta-analytic observational study, systematic review and meta-analysis to determine the effect of isotretinoin for acne vulgaris therapy on laboratory values. A total of 17 studies were included in the qualitative review (systematic review) and 17 studies of which can be conducted quantitative review (meta-analysis) Two studies that were not included in the meta-analysis study were the Ertugrul 2010 and Soyuduru 2018 because of different outcome units.

The age range of samples varies with each study that goes into systematic and metaanalysis reviews. Age range of 17-44 years in Sarac study, 15-45 years on Gencoglan study, 16-45 years on Onder study, 18-37 years on Tamer study, 12-39 in Ahmad study, 18-35 years on Yaldiz study, 18-30 years on Ataseven study, 15-37 in Bugdayci study, 18-38 years in Ertugul, 18-34 years Saklamaz, 18-30 years in Ozkol study, 12-24 years in Soyuduru study, 16-25 years in Cemil, 15-45 in the Centikaya study, 15-40 in the Karadag study. The age range of samples varies with each study that goes into systematic and metaanalysis reviews. Age range of 17-44 years in Sarac study, 15-45 years on gencoglan study, 16-45 years on Onder study, 18-37 years on Tamer study, 12-39 in Ahmad study, 18-35 years on Yaldiz study, 18-30 years on Ataseven study, 15-37 in Bugdayci study, 18-38 years in Ertugul, 18-34 years Saklamaz, 18-30 years in Ozkol study, 12-24 years in Soyuduru study, 16-25 years in Cemil, 15-45 in the Centikaya study, 15-40 in the Karadag study. According to literature, acne presents in about 85% of young people between the ages of 12 to 24, can persist until adolescence adulthood, or can arise after the teenage period. [4,23]

Studies included the dose of isotretinoin in the range of 0.2-1 mg /kg/day. Literature recommends the dose for severe papulopustular acne / moderate nodular acne are 0.3-0.5 mg / kg. The dose starts from the personalized low dose (0.1–0.2 mg/kg/day) of isotretinoin and further increases to the highest tolerable dose or even intermittent therapy. Severe nodular/conglobatae acne, especially for severe chest and back involvement, higher doses (≥0.5 mg/kg) of systemic isotretinoin are indicated. [24]

The monitoring period is at least 4 weeks after therapy. Based on the literature in oral isotretinoin use, a 50% reduction in pustules can be expected after 2−4 weeks of treatment. [24] Clinical monitoring is usually carried out in conjunction with laboratory monitoring. Patients with malignancy and systemic diseases such as liver, kidney and hematological disorders were not involved in the study because of the abnormal baseline.

Analysis on triglyceride values showed in Sarac 2020, Kutlu 2019, Onder 2020, Tamer 2019, Yaldiz 2018, Bugdayci 2016, Ertugrul 2010, Ozkol 2014, Soyuduru 2018, Ahmad 2015, Saklamaz 2016, Cemil 2016, Centikaya 2019, Karadag 2010, which significant increase of triglyceride value. Metaanalysis results showed the mean difference between baseline and after therapy (15.66 weeks) was 25.81 mg/dL (95% CI, 19.87 – 31.74 mg/dL). The National Institutes of Health Clinical Center explains the high risk value of triglycerides is 200 mg/dL. References based on The Common Terminology Criteria for Adverse Events show a grade 1 value of 150 mg/dL-300 mg/dL, at grade 2 of 300 mg/dL-500 mg/dL. The results of metaanalysis, the lowest score is 84.42 ± 31.61, while the highest is 121.54 ± 54.99, where neither had high risk nor reached grade 1 for CTCAE criteria. Bugdayci 2016 and Soyuduru 2018 studies, was not conducted meta-analysis because lack of data. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case triglyceride values.

Analysis of total cholesterol values, in Onder 2020, Tamer 2019, Ahmad 2015, Yaldiz 2018, Bugdayci 2016, Ertugrul 2010, Saklamaz 2016, Ozkol 2014, Soyuduru 2018, Cemil 2016, Centikaya 2019, Karadag 2010, Sarac 2020, Kutlu 2019 showed a significant increase in value. The results of the meta-analysis showed the mean difference between baseline and period after therapy (15.71 weeks) was 16.11 mg/dL (95% CI, 13.04 – 19.18 mg/dL). Z=8.52, P<0.00001, differ significantly. The highest value was 192.5 ± 35.5 mg/dL, while the lowest value was 161.61±34.75 mg/dL. Reference values from The National Institutes of Health Clinical Center on high-risk total cholesterol are 240 mg/dL. References based on The Common Terminology Criteria for Adverse Events show a grade I value of 201-300 mg/dL; Grade II 301-400 mg/dL. In the meta-analysis, the the scores did not show high risk and had not reached grade I based on CTCAE. The results were in accordance with the hypothesis, that isotretinoin had an effect on laboratory values, in this case the value of total cholesterol.

Analysis of Low-Density Lipoprotein Cholesterol values in Onder 2020, Tamer 2019, Yaldiz 2018, Ertugrul 2010, Saklamaz 2016, Ozkol 2014, Soyuduru 2018, Cemil 2016, Centikaya 2019, Karadag 2010, Kutlu 2019 showed significant improvement. In the results of the meta-analysis, the mean difference between baseline and period after therapy (14.8 weeks) was 15.11 mg / dL (95% CI, 11.36-18.85 mg /

dL). Z = 7.91, p = < 0.00001, significantly different. The value in the lowest meta-analysis is 87.02±27.87 mg/dL, and the highest value was 121.8 ± 37.3 mg/dL Reference value from The National Institutes of Clinical Health Center on high-risk LDL was 160 mg/dL. In the meta-analysis, LDL values is not show a high risk. The results are in accordance with the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of total cholesterol.

Analysis of high-density lipoprotein cholesterol values in Onder 2020, Yaldiz 2018, Saklamaz 2016, Ozkol 2014, Soyuduru 2018, Centikaya 2019, Karadag 2010, Kutlu 2019 showed a significant decrease, while neither Cemil 2016 nor Ertugrul 2010, was have the significant decrease. Tamer study 2019 shown an increase in value. The meta-analysis found the mean difference between baseline and period after therapy (14.8 weeks) was -3.09 mg/dL (95% CI, -4.71 to -1.48 mg/dL). Z= 3.76, p =0.0002, differ significantly. The mean value in the lowest meta-analysis was 42.63 ± 6.98 mg/dL, and the highest value was 55.2 ± 11.6 mg/dL. Reference values from The National Institutes of Health Clinical Center on high-risk LDL are 160 mg/dL. In the meta-analysis, LDL values did not show a high risk. The results are in accordance with the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of total cholesterol.

Analysis of Aspartate Aminotransferase value in Sarac 2020, Kutlu 2019, Yaldiz 2018, Bugdayci 2016, Ertugrul 2010, Ahmad 2015, Centikaya 2019, Karadag 2010 showed significant improvement, while in the 2014 Ozkol study the increase was insignificant. The results of the meta-analysis found the mean difference between baseline and after therapy (17 weeks) was 3.08 U /L (95% CI, 2.04 to 4.13 U / L), Z = 5.80. P= 0.00001, differs significantly. The mean value on the lowest meta-analysis is 18.2 ± 3.6 U/L, and the highest value is 24.9 ± 8.69 U/L. Ertugrul's study cannot be included in metaanalysis because lack of data. References based on The Common Terminology Criteria for Adverse Events in AST show grade I values of 41-100 U /L, grade II of 108 U / L. In the meta-analysis, the AST value obtained is not in grade I based on CTCAE. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of AST.

Alanine Aminotransferase value analysis in Sarac 2020, Kutlu 2019, Ozkol 2014, Centikaya 2019, experienced an insignificant increase. Bugdayci 2016, Ertugrul 2010, Ahmad 2015 showed a significant increase, while in the Yaldiz 2018 there was a significant decrease. Karadag 2010 showed improvement but was not specific. The mean difference between baseline and period after therapy (17 weeks) was 1.61 U/L (95% CI, -0.07 to 3.03 U/L). Z = 1.87, p = 0.06, was no different significantly. The mean value in the lowest meta-analysis is 13.4 ± 4.7 U/L, and the highest value is 24.4 ± 15.8 U/L. The Ertugul study cannot be assessed because it did not have a standard deviation. References based on The Common Terminology Criteria for Adverse Events on ALT show a grade II value of 111 U/L. In the meta-analysis, the ALT value obtained was not grade II based on CTCAE. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case alt values.

The hemoglobin analysis in the Seckin 2015 shows a significant increase, while Kutlu 2019, Ataseven 2014 increased significantly and Karadag 2010 experienced inspecific increase. The mean difference between baseline and after therapy (12 weeks) was 0.18 g/dL (95% CI, -0.07 to 0.42 g/dL). Z=1.40, P=0.16, insignificant. The mean value in the lowest meta-analysis is 13.9 ± 2.8 g/dL, and the highest value was 14.25± 1.42 g/dL. References based on The Common Terminology Criteria for Adverse Events on Hb indicate a grade II value when it was less than 10 to 8 g/dL. In the meta-analysis, hb values obtained was not grade II based on CTCAE. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case hb values.

WBC analysis in Sarac Study 2015, Seckin 2015, Onder 2020, Ataseven 2014 experienced an insignificant decrease, Gencoglan 2017 and Tamer 2019 show a significant decrease while Kutlu 2019 experienced an insignificant increase. The mean value in the lowest meta-analysis was 6.91 ± 1.6 x103/µL, and the highest value of 7.92 ± 2.04 x103/µL. The mean difference between baseline and the period after therapy (12 weeks) was -0.23 x103/µL (95% CI, -0.42 to - 0.04 x103/µL) Z= 2.38, p = 0.02, significantly different. References based on The Common Terminology Criteria for Adverse Events on leukocytes indicate a grade III value when >100,000/mm3. In the meta-analysis, the WBC value obtained was not grade III based on CTCAE. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case WBC values.

Analysis of PLT values in the Gencoglan 2017 and Ataseven 2014 show a significant decrease. Kutlu 2019 and Onder 2020 experienced an insignificant increase. Seckin 2015, had significant improvement. The mean value in the lowest meta-analysis was 255.1 ± 60.3µL, and the highest value was 255.1 ± 60.3/µL. The mean difference between baseline and period after therapy (11.2 weeks) was -1.85 x103/µL (95% CI, -6.21 to 9.91 x103/µL). Z=0.45, P= 0.65, insignificant. Normal platelet value 150-400 x103 /µL. In the meta-analysis, the value of the obtained PLT increased but was in normal range according to the hypothesis, that isotretinoin has an effect on laboratory values, in this case PLT values.

MPV analysis in Seckin 2015, Gencoglan 2017 show an insignificant increase in mean, Onder 2020 experienced a significant increase while Kutlu 2019, Ataseven 2014, Tamer 2019 experienced a significant decrease. The mean difference between baseline and period after therapy (11.3 weeks) was -0.09 fL (95% CI, -0.41 to 0.22 fL). Z=0.58, P= 0.56, insignificant. The mean value in the lowest meta-analysis was 8.5±0.9 x103 /µL, and the highest value is 9.47±1.3 x103 /µL. Normal MPV value of 4-11 fL. In the meta-analysis, MPV values increased but were still normal. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case MPV values. Analysis of lymphocytes in Onder 2020, Gencoglan 2017 show an insignificant increase, Tamer 2019 experienced a significant decrease. Kutlu 2019 has increased significantly. The mean difference value between baseline and period after therapy (11 weeks) was 0.01 x103/µL (95% CI, -0.20 to 0.21 x103/µL). Z=0.05, P=0.96, insignificant. The mean value in the lowest meta-analysis was 2.14±0.49x103 /µL, and the highest value was 2.67±1.07x103 /µL. The normal value of absolute lymphocyte count was 0.8 - 4 x x103 /µL. In the meta-analysis, MPV values increased but were still normal. The results were in accordance with the hypothesis that isotretinoin has an effect on laboratory values, in this case lymphocyte values.

Monocyte analysis in Onder 2020, Gencoglan 2017, Kutlu 2019 show an insignificant increase in mean, Tamer 2019 experienced an insignificant decrease. The mean difference between baseline and period after therapy (11 weeks) was 0.01 $x10^3$/µL (95% CI, -0.01 to 0.03 x103/µL). Z=1, P=0.32, insignificant. The mean value in the lowest meta-analysis was 0.51 ± 0.14 x103/µL, and the highest value was 0.56±0.21x103 /µL. The normal value of absolute monocyte count 0.1 – 0.9 x x103 /µL. In meta-analyses, monocyte values increase but were still normal. The results were in accordance with the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of monocytes.

Basophil analysis in Tamer 2019 and Kutlu 2019 experienced an insignificant decrease in mean, Gencoglan 2017 experienced an insignificant increase. The mean difference between baseline and period after therapy (10.6 weeks) is decrease 0.00 x103/µL (95% CI, -0.02 to 0.01 x103/µL). Z= 0.25, P=0.8, insignificant. The mean value in the lowest meta-analysis was 0.03±0.06x103/µL, and the highest value was 0.07 ± 0.02x103/µL. Normal value of absolute basophil count 0-0.1 x x103 /µL. In the meta-analysis, the value of basophils decreased but was still normal. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of basophils.

Eosinophil analysis in Tamer 2019 experienced an insignificant decrease in mean, Gencoglan 2017 experienced an insignificant increase. Kutlu 2019 decreased significantly. The mean difference between baseline and period after therapy (10.6 weeks) was 0.00 $x10^3$/µL (95% CI, -0.01 to 0.02 $x10^3$/µL). Z= 0.19, P =0.85, insignificant. The mean value in the lowest meta-analysis was 0.12±0.908 $x10^3$ /µL, and the highest value was 0.18±0.19 x $10^3$/µL. The normal value of the eosinophil absolute count is 0–0.7 × $10^3$/µl. In the meta-analysis, eosinophil values increased but were still normal. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case eosinophil values.

Neutrophyl analysis in Tamer 2019 and Kutlu 2019 experienced an insignificant decrease in mean, Gencoglan 2017 and Onder 2020 experienced a significant decrease. The mean difference between baseline and period after therapy (11 weeks) was decrease 0.26

$x10^3/\mu L$ (95% CI, -0.48 to -0.04 $x10^3/\mu L$). Z= 2.29, P=0.02, was significant. The mean value in the lowest meta-analysis was 3.89 ± 1.29$x10^3$ /µL, and the highest value was 4.65±1.90 x $10^3$ /µL. The normal value of absolute neutrophyl count 2-7 $x10^3$ × $10^3$/µl. In the meta-analysis, neutrophyl values decreased, but were still normal. The results correspond to the hypothesis, that isotretinoin has an effect on laboratory values, in this case neutrophyl values.

Fasting glucose analysis in Saklamaz 2016, Ozkol 2014, Ertugul 2010, show an insignificant increase in mean, Cetinozman 2013 decreased insignificantly, Karadag 2010 decreased. The mean difference between baseline and period after therapy (13 weeks) was 0.55 mg/dL (95% CI, -1.47 to 2.56 mg/dL). Z = 0.53, p = 0.60, insignificant. The mean value in the lowest meta-analysis was 87.4±9.0 mg/dL, and the highest value was 90.69 ± 9.85 mg/dL. But Cetinozman's 2013 study could not be meta-analyzed because it did not have an SD value. Normal values ≥ 7 years: 70 - 100 mg / dL. In the meta-analysis, fasting blood glucose values increased but were still normal. The results are in accordance with the hypothesis, that isotretinoin has an effect on laboratory values, in this case the value of fasting glucose.

Analysis HOMA IR in Ertugrul 2010, Saklamaz 2016, Cetinozman 2013 show an insignificant increase in mean, Soyuduru 2018 experienced a significant increase. Normal value <4. All studies cannot be meta-analyzed because there were 2 studies that do not have an SD value. Based on the studies collected, all experienced had improvements, but still in normal range. The results were accordance with the hypothesis, that isotretinoin has an effect on laboratory values in this case the HOMA IR value.

The most common laboratory disorder was an increase in triglycerides. Elevation of triglycerides will increase the potential risk of atherosclerosis, as well as pancreatitis induced hypertriglycerride. Recommendations that can be given if there is an elevation of moderate triglyceride values (300–500 mg / dL), such as increase physical activity, weight loss, a low-fat, low-carbohydrate, low-alcohol diet. Omega-3 fatty acid supplements may provide benefits in the treatment of oral isotretinoin. When triglyceride levels are more than 500 mg/dL, the dose of isotretinoin can be lowered, accompanied by lifestyle and dietary changes. If triglyceride levels remain elevated, lipid-lowering agents may be needed (such as derivates of fibratic acid, niacin, or statins). Triglyceride elevation >800 to 1000 mg/dL can cause pancreatitis, so isotretinoin may be discontinued until lipids are better managed. If there is a two to threefold increase in the transaminase value, a decrease in the dose may be considered. Re-examination can be done in 2 weeks. Discontinuation of isotretinoin, may be possible if there is no improvement. [25]

## CONCLUSION

The results of the meta-analysis shows that oral isotretinoin intake significantly affects laboratory changes of AST, lipid profile (triglycerides, total cholesterol, LDL, HDL), *Complete Blood Count* (WBC, netrofil) significantly. Parameters of ALT, *Complete Blood Count* (Hb, PLT, MPV, lymphocytes, monocytes, basophils, eosinophils), Fasting glucose had a change but not significant. Most of the parameters in the study shows significant changes, except for the *Complete Blood Count*. HOMA IR parameters is excluded in metaanalysis, but included in systematic review study. All laboratory changes in the study still do not require a decrease in dose or discontinuation of therapy. The use of isotretinoin in triglycerides parameter study for 15.66 weeks, total cholesterol for 15.71 weeks, LDL 14.8 weeks, HDL 14.8 weeks, AST 17 weeks, ALT 17 weeks, Hb 12 weeks, WBC 12 weeks, platelets 11.2 weeks, MPV 11.3 weeks, lymphocytes 11 weeks, monocytes 11 weeks, basophils 10.6 weeks, eosinophils 10.6 weeks, netrophiles 11 weeks, and GDP 13 weeks result in a change in value. Various studies collected show that isotretinoin intake at dose of 0.2-1 mg /kg is do not cause significact changes, therefore the time for laboratory evaluation can be extended. Longer laboratory evaluation time, can reduce the cost of treatment and discomfort of patients in acne therapy. Acne patient with abnormal baseline values of laboratory parameters should avoid taking oral isotretinoin.

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**Conflict of Interest**

There is no conflict of interest

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