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# Correlation between Cytochrome P450, 5-alpha Reductase, and Androgen Receptor Levels in Patients with Type 2 Diabetes Mellitus

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## Abstract

**Objective:** Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases**.** The CYP450 plays an important role in the biosynthesis of steroid hormones and the hormonal activity is mediated by the androgen receptor (AR) and the enzyme 5-alpha reductase (5αR). Therefore, this study aimed to investigate the relationship between these factors in T2DM.

**Materials and Methods:** This case-control study was performed with 60 volunteers, including 30 diabetics and 30 healthy individuals. Demographic information of individuals was recorded and levels of CYP450, 5αR, and AR were measured in serum by ELISA. Data were analyzed by SPSS v.26 version and the significance level was less than 5%.

**Results:** There were no significant difference between diabetics and healthy individuals in gender (*P*= 1), body mass index (*P*= 0.199), diastolic pressure(*P*= 0.466), uric acid(*P*= 0.202), creatinine(*P*= 0.627), low-density lipoprotein (*P*= 0.572), high-density lipoprotein(*P*=0.692); But there was a significant difference in systolic pressure(*P*= 0.034), triglyceride(*P*= 0.0001), and insulin(*P*= 0.003), between diabetics and healthy individuals. The distribution of CYP450, 5αR and AR in two groups shows that the level of all three factors is higher in diabetic people (*P*= 0.0001). Also, glycosylated hemoglobin and insulin have a direct relationship with CYP450 (*P*= 0.0001, R=0.494; *P*= 0.043, R=0.263), 5αR (*P*= 0.0001, R=0.808; *P*= 0.016, R=0.309) and with AR (*P*= 0.0001, R=0.836; *P*= 0.011, R=0.326).

**Conclusion:** These results showed that there was a relationship between the levels of CYP450, 5αR, and ARs with T2DM which may explain hormonal changes in diabetic people and the different responses to treatment.

**Keywords**: Diabetes mellitus, Cytochrome P450, 5-alpha reductase, Androgen receptor

QR Code:

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## Introduction

The increasing incidence of diabetes is a major concern because of its association with many metabolic diseases (1). Hyperglycemia due to impaired insulin secretion, insulin function, or both can lead to diabetes mellitus (2). Overweight and obesity are the most important risk factors for diabetes (2).

Unlike many single-gene diseases, in which only one gene defect is the main cause of the disease, in diabetes, several genes are involved in causing the disease, some of which are not yet identified. So far more than 40 genes have been identified in connection with diabetes. The highest number of substrates among cytochrome P450 (CYP450) enzymes belongs to CYP3A4 gene, which has been identified in connection with diabetes (3). CYP450 is one of the drug-metabolizing enzymes that changes in the functional activity of these enzymes can cause a variable response to some drugs in diabetic patients (4). CYP450 plays an important role in the oxidation of organic matter, the biosynthesis of steroid and lipid hormones, the metabolism of most drugs, and other xenobiotics (5). CYP450 are enzymes that play a key role in steroid metabolism, and there are hypotheses that sex hormones and diabetes may be linked. Some studies have examined the expression of CYP450 in T2DM alterations and confirmed their association (6,7).

The link between obesity and diabetes is not only associated with several clinical problems, but studies have shown that obesity and diabetes are directly related to the incidence of reproductive disorders (8,9). Diabetes is closely related to gonadal endocrine activity, so that abnormal glucose metabolism may affect the activity of the hypothalamic-pituitary-gonadal axis and lead to sex hormone disorders (10). Diabetes has an inhibitory effect on the activity of the hypothalamic-pituitary-gonadal hormone axis, thereby reducing the serum levels of testosterone and gonadotropins (11).

Decreased androgen production is associated with reduced levels of gonadotropins in the blood (12). Testosterone (the most well-known androgen) has been identified in various studies as an anti-diabetic hormone, and there is evidence that low testosterone is associated with obesity, T2DM, and metabolic syndrome (13). It has also been shown that the enzyme 5-alpha reductase (5αR) and androgen receptor (AR) affect the hormonal activity of androgens. 5αR converts testosterone to dihydrotestosterone (DHT) and plays a major role in three metabolic pathways including bile acid biosynthesis, metabolism of androgen, and estrogen (14). Performing physiological functions of testosterone and DHT requires their binding to the AR. This binding regulates the transcription of target genes. Androgens are an important factor in inhibiting fat deposition in the body. Epidemiological studies confirm a significant association between low testosterone levels and obesity in men and low testosterone levels have been shown to cause intra-abdominal fat accumulation, central obesity and an increased risk of metabolic syndrome in men (15,16).

Since previous studies have detailed testosterone and its association with diabetes, but studies of factors affecting sex hormones and their association with diabetes are not enough, so for the first time, three factors affecting sex hormones include 5αR, CYP450, and ARs have been studied and their relationship to T2DM has been assessed.

Therefore, the aim of this study was to examine the correlation between CYP450, 5αR, and AR in T2DM compared to the control group.

## Materials and Methods

### Study design

A case-control study was designed on 60 samples, including 30 T2DM and 30 healthy volunteers.

The sample size was calculated for a significant difference between the two groups,



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with a power of 80% and an alpha value of 0.05 from the two independent student test formula based on the study by Mattack et al. (17). Therefore, the required sample size (n=30 subjects per group) was obtained.

## Setting

This study was done in Mashhad (Iran) in 2020. The statistical population included 30 people with T2DM referred to Imam Reza Hospital, whose disease has been approved by an internal medicine specialist or endocrinologist, and 30 healthy volunteers who have been proven not to have diabetes by two blood sugar tests. Demographic information including age, sex, height, weight, BMI, Exercise-intensity, tobacco distribution, diastolic and systolic blood pressure were assessed and recorded.

## Participants

The participants included in this study were over the age of 25 years. Additionally, in this study, pairing was done in two groups in terms of gender. Patients with a history of acute illness such as chronic liver and kidney disease, pregnancy, lactation, a history of cancer, malnutrition, and taking drugs that affect insulin and glucose levels were excluded from the study. An informed consent form was received from all participants.

## Variables

In this study, blood factors such as fasting blood sugar (FBS), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), total cholesterol (Chol), glycosylated hemoglobin (HbA1C), creatinine (Cr), uric acid (UA), and insulin levels were evaluated and compared in the two groups.

## Measurements

CYP450, 5αR and ARs were measured using ELISA commercial kits made in Germany (Zellbio).

For this purpose, blood samples were collected in sterile tubes (5ml) and incubated at room temperature (15-25 °C) for at least 15 minutes. Then centrifuged at 10,000 rpm for 10-15 minutes and isolated serum was used for experiments. CYP450, 5αR, and ARs were measured using a common protocol with slight differences in the second step. In order to measure the level of CYP450, after preparing reagents, samples, and standards, first mix 40 µl of serum sample, 10 µl of CYP3A4-AB, 50 µl of standard solution and 50 µl of streptavidin-HRP together and incubated for 60 minutes at 37 ° C. Then, for washing the plate, 300 microliters of washing buffer was added. In the next step, 100 µl of chromogen solution was added and incubated for 37 minutes at 37 ° C for staining. Then 50 µl of stop solution was added and the absorbance was measured at 450 nm for 10 min. In the measurement of 5αR in the second stage SRD5A1A-AB replaces CYP3A4-AB and in the measurement of ARs AR-Ab replaces CYP3A4-AB.

## Statistical methods

Appropriate tables and statistical indicators (such as mean and standard deviation) have been used to indicate data. First, normal distribution was examined by the Shapiro-Wilk test. When abnormal data was observed the Mann-Whitney test was used and for confirmation of normality, appropriate parametric methods such as student-test were used. A Chi-square test was used to analyze the data with a nominal scale. The Pearson correlation coefficients were used to summarize the relationship between two data samples. The outputs were produced using SPSS v.26 version. A *P* less than 5% is statistically significant. (In the results, values less than 5% are marked with a "*" sign and values less than 1% are marked with a "**" sign).

## Ethical considerations

The local Ethics Committee affiliated with Islamic Azad University, Mashhad Branch (Medical Sciences) approved this study (Registration code: IR.IAU.MSHD.REC.1396.112).

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All the participants provided their informed written consent for participation in the present study.

## Results

### Descriptive data

In this study, 30 individuals with T2DM and 30 healthy individuals participate (46.6% men and 53.3% women; each group). The baseline characteristics of two studied groups showed in Table 1. Also, normal distribution of frequencies and percentage of blood parameters in control group is: FBS 25 (83.3%); HbA1c 28(93.3%); Chol 23(76.7%); TG 30(100%); HDL 9(30%); LDL 16(53.3%); Cr 10 (33.3%); UA 25 (83.3%); Insulin 30 (100%); And the seem for diabetic group is: FBS 9 (30%); HbA1c 0 (0%); Chol 30 (100%); TG 30 (100%); HDL 11 (36.7%); LDL 13 (43.3%); Cr 16 (53.3%); UA 24 (80%); Insulin 24 (80%).

### Main results

CYP450 distribution in control and patient samples are shown in Figure 1, the mean CYP450 level in the diabetic patients and the control group were 6.42 (± 2.72) ng/ml and 3.45 (± 1.69) ng/ml, respectively. CYP450 level is higher in diabetics and there is a significant difference between this factor in control and diabetic patients (*P*= 0.0001), (Figure 1).

Figure 2 shows the distribution of 5αR in control and case groups. The mean 5αR level in the diabetic group and the control group were 20.57 (± 5.19) ng/ml and 4.79 (± 1.44)

**Table 1. Demographic data and blood indices distribution in diabetic and control groups**

| Variable | Control Mean(±SD) | Diabetes Mean(±SD) | *P* * |
|---|---|---|---|
| **Age (year)** | 48.53 (± 10.36) | 52.90 (± 10.38) | 0.108 |
| **BMI (kg/m$^2$)** | 28.11 (± 3.73) | 29.55( ± 4.80) | 0.199 |
| **Diastolic pressure (mmHg)** | 89.0 ( ± 14.70) | 91.67 (± 13.41) | 0.466 |
| **Systolic Pressure (mm Hg)** | 130.67 (± 16.17) | 138.77 (± 12.47) | 0.034 |
| **FBS (mg/dl)** | 95.93 (± 16.43) | 128.33 (± 17.92) | 0.0001 |
| **HbA1c (%)** | 5.02 (± 0.57) | 7.42 (± 0.60) | 0.0001 |
| **Chol. (mg/dl)** | 177.60 (± 50.27) | 183.43 (± 5.02) | 0.530 |
| **TG (mg/dl)** | 125.33 (± 18.13) | 168.13 (± 10.40) | 0.0001 |
| **HDL (mg/dl)** | 43.37 ( ± 14.48) | 45.12 (± 19.29) | 0.692 |
| **LDL (mg/dl)** | 101.77 (± 33.77) | 106.88 (± 35.91) | 0.572 |
| **Cr (mg/dl)** | 1.05 (± 0.25) | 1.02 (± 0.24) | 0.627 |
| **Uric Acid (mg/dl)** | 5.67 ( ± 0.88) | 5.92 (± 0.59) | 0.202 |
| **Insulin (µu/ml)** | 3.49 (± 2.15) | 13.55 (± 16.64) | 0.003 |

* Statistical test: T-test

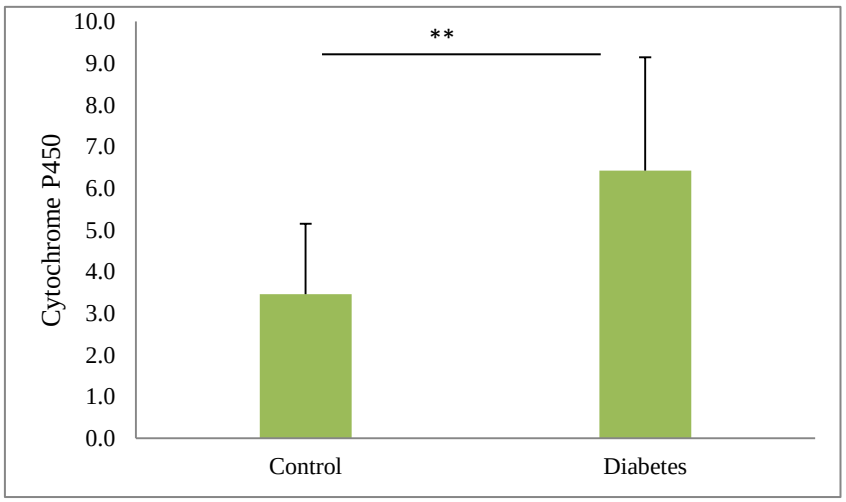


**Figure 1. Cytochrome P450 distribution (ng/ml) in patients with T2DM and controls. (Results showed Mean ±SD; *P*= 0.0001**)**



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ng/ml, respectively. The level of 5αR is higher in diabetics and there is a significant difference between control and case groups (*P*= 0.0001).

ARs distribution in the control and diabetic groups are shown in Figure 3. The mean ARs level in the diabetic and the control groups were 21.51 (± 2.59) ng/ml and 9.38 (± 3.96) ng/ml, respectively. As can be seen, ARs level is higher in diabetics and there is a significant difference between the levels in the control and case groups (*P*= 0.0001).

## Correlation of CYP450, 5-alpha reductase, and AR with blood markers

As shown in Table 2, there is a significant correlation between CYP450 with FBS (*P*= 0.004), HbA1c (*P*= 0.0001), TG (*P*= 0.0001) and Insulin (*P*= 0.043) in the total value. Also, there is a significant correlation between 5αR levels and FBS (*P*= 0.0001), HbA1c (*P*= 0.0001), TG (*P*= 0.0001) and insulin (*P*= 0.016) in the total value. In addition, there is a significant correlation between AR and FBS (*P*= 0.0001), HbA1c (*P*= 0.0001) and TG (*P*= 0.0001), insulin (*P*= 0.011) and age (*P*= 0.011) in the total value.

**Table 2. Correlation of cytochrome P450, 5-Alpha reductase, and Androgen receptor in overall with indexes**

| Variable | CYP450 | | 5-Alpha reductase | | Androgen receptor | |
|---|---|---|---|---|---|---|
| | Correlation coefficient (R) | *P* | Correlation coefficient (R) | *P* | Correlation coefficient (R) | *P* |
| **Age** | 0.168 | 0.201 | 0.243 | 0.062 | 0.325 | 0.011 |
| **BMI** | 0.127 | 0.332 | 0.145 | 0.269 | 0.231 | 0.076 |
| **Systolic pressure** | 0.144 | 0.272 | 0.213 | 0.103 | 0.205 | 0.115 |
| **Diastolic pressure** | 0.030 | 0.819 | 0.028 | 0.831 | 0.032 | 0.808 |
| **FBS** | 0.367 | 0.004 | 0.597 | 0.0001 | 0.568 | 0.0001 |
| **HbA1c** | 0.494 | 0.0001 | 0.808 | 0.0001 | 0.836 | 0.0001 |
| **Total Cholesterol** | -0.040 | 0.764 | 0.119 | 0.367 | 0.146 | 0.267 |
| **Triglyceride** | 0.499 | 0.0001 | 0.745 | 0.0001 | 0.755 | 0.0001 |
| **HDL** | -0.066 | 0.615 | 0.075 | 0.567 | 0.044 | 0.739 |
| **LDL** | 0.011 | 0.933 | 0.166 | 0.206 | 0.106 | 0.419 |
| **Uric acid** | 0.078 | 0.556 | 0.150 | 0.253 | 0.036 | 0.783 |
| **Serum Creatinine** | 0.020 | 0.881 | -0.138 | 0.292 | -0.108 | 0.410 |
| **Insulin** | 0.263 | 0.043 | 0.309 | 0.016 | 0.326 | 0.011 |

* Statistical test: Pearson Correlation

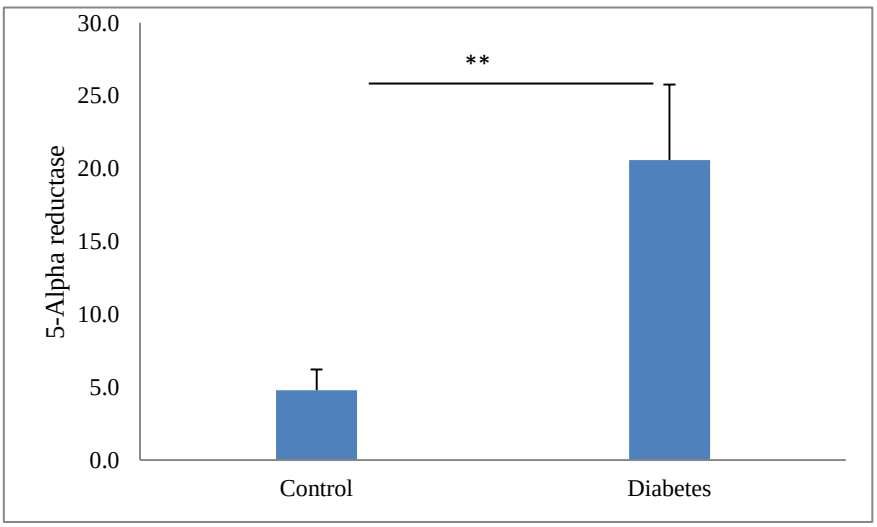


**Figure 2. 5-Alpha reductase distribution (ng/ml) in patients with T2DM and controls. (Results showed Mean ±SD; *P*= 0.0001**)**



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## Correlation of CYP450 with 5αR and AR

The correlation of CYP450 with 5αR and AR in the diabetic and control groups are listed in Table 3. As can be seen, there is a significant difference between CYP450 levels with 5αR (*P*= 0.0001) and ARs (*P*= 0.0001).

## Correlation of 5αR with ARs

Also, Table 3 shows the relationship between 5αR and AR parameters in patients and controls. In total, there is a significant difference between these two factors (*P*= 0.0001).

## Discussion

Diabetes mellitus is a chronic disease whose global prevalence is rapidly increasing (18). Studies have shown that obesity and T2DM are strongly linked (19). In the present study, we investigated the level of CYP450, 5αR, AR, and their relationship in people with T2DM compared to the control group. The result showed that the level of CYP450, 5αR, and ARs increased significantly in the diabetic group compared to the control group. Table 2 showed that there is a significant relationship between the level of CYP450, 5αR, and AR with blood parameters like triglycerides, HbA1c, FBS, and insulin in general. Also, Table 3 showed that there is a correlation between 3 factors CYP450, 5αR, and the AR comparing the two groups. Therefore, our results showed that there is a significant relationship between these 3 factors studied as well as a relationship between them and the main parameters of T2DM.

Our results concerning blood parameters such as HbA1c, TG, insulin, UA (Table 1) were confirmed by other studies (20-22).

Dindas et al. studied testosterone levels in patients with obesity and T2DM. The study conducted on 1,842 men (1,451 non-diabetics and 328 diabetics), found that 51 % of obese men with diabetes under 45 years had low levels of free testosterone. In this case, it can

**Table 3. Correlation between 3 factors CYP450, 5-α reductase, and androgen receptor comparing the two groups**

| Correlation (between two variables) | Controls | | Diabetes | | Total | |
|---|---|---|---|---|---|---|
| | Correlation coefficient (R) | *P* | Correlation coefficient (R) | *P* | Correlation coefficient (R) | *P* |
| **CytP450 / 5-Alpha reductase** | -0.118 | 0.533 | 0.451* | 0.012 | 0.628** | 0.0001 |
| **CytP450 / Androgen receptor** | 0.160 | 0.399 | 0.062 | 0.744 | 0.528** | 0.0001 |
| **5-alpha reductase / Androgen receptor** | 0.361* | 0.050 | 0.087 | 0.649 | 0.820** | 0.0001 |

* Statistical test: Pearson Correlation

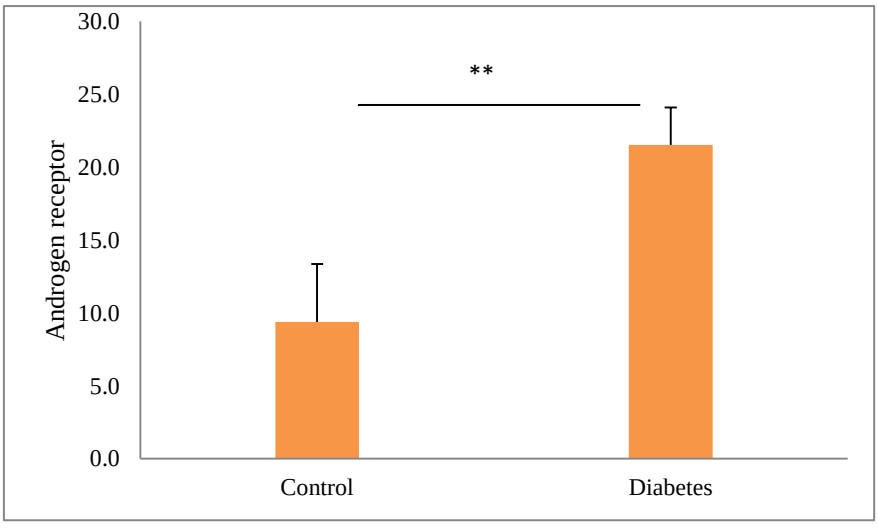


**Figure 3. Androgen receptor distribution (ng/ml) in patients with T2DM and controls. (Results showed Mean ±SD; *P*= 0.0001**)**



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be argued that obesity is probably associated with low testosterone levels in men and that obese diabetics had lower testosterone concentrations (23).

The results of a survey in 2010 show that the association between CYP2J2 G-50T polymorphism and T2DM risk may change with age, family history, and obesity.CYP2J2 G-50T polymorphism in patients with early-onset T2DM with effects on insulin resistance may contribute to the pathogenesis of T2DM (24). Ruzilawati and Bustos showed that mutations in the CYP3A4 genes reduced CYP450 levels, so in patients insulin level is lower than healthy individuals (25). Our findings are consistent with the above researches. Another study was conducted in 2018 to investigate the effects of T2DM on the expression and activity of major CYP450s (4). T2DM can modulate CYP450 actions in the metabolism of drugs and cardiovascular homeostasis. Dostalek et al. investigated the effect of diabetes on CYP450. These studies indicate the association between diabetes and a significant reduction in hepatic P450 enzymatic activity and protein level (26**).** The results of the above study do not match with our results and this discrepancy may be related to the test conditions.

The harmful effects of obesity and T2DM on various organs of the body have been studied by researchers, and reports indicate that the effects can disrupt the function of various organs of the body, including hormones and the reproductive system, by producing free radicals and thus increasing lipid peroxidation (27).

One of the treatment problems is age-related estrogen or androgen lack in obesity and T2DM. Estrogen can maintain homeostasis of energy through estrogen receptor alpha (Erα) and estrogen receptor beta (Erβ) by suppressing energy intake and lipogenesis, increasing energy consumption, and increasing insulin secretion and sensitivity. In men, testosterone is changed to estrogen and fuel homeostasis is maintained through ERs and AR, thereby performing their related functions to suppress adipose tissue accumulation and increase insulin sensitivity (28). Our results also showed that the amount of ARs in diabetics showed a significant increase compared to the control group, so as discussed in the above study suppression of this factor may reduce the risk of developing diabetes.

Low concentrations of endogenous androgens are also associated with insulin resistance and atherosclerosis. Serum testosterone concentrations have been reported to be lower in diabetics than non-diabetics (29). In a study, Fukui et al. found that serum testosterone concentrations in Japanese T2DM patients were much lower than in healthy individuals (30). Mattack et al. examined the association between testosterone levels and T2DM in men in northeastern India. The results of this study showed that total testosterone, free testosterone, and sex hormone-binding globulin in the test group were considerably lower than in the control group. FBS also shows a negative correlation with total and free testosterone (17).

The study which was done in 2016 (31) showed that the use of 5αR inhibitor can reduce the five-year risk of diabetes in benign prostate hyperplasia (BPH) patients under 65 years. Similarly, the results of another study in 2014 showed the positive effect of the use of 5αR inhibitors in the incidence of diabetes (32). These results are consistent with the present study. Distribution of CYP450, 5αR and ARs levels in control and patients shows that there is a significant difference between their level in control and diabetic. Also, 5αR has a direct relationship with AR in control and diabetic groups. Our results were confirmed by Chung et al. (33) and Al-Kuraishy studies (34).

Since the present study was carried out during the corona pandemic, it was cross-sectional with a small number of patients and limited to one hospital, and this study may be carried out in the future in several hospitals with more patients. In addition, more parameters can be verified by monitoring patients over a period of time. As a suggestion



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for further studies, it can be done in a multi-center with a larger sample size, and also the level of CYP450, 5αR, and AR in patients with diabetic nephropathy can be examined. In addition, it is recommended that in subsequent studies, both patient and control groups be followed up within 6 months.

## Conclusions

Diabetes is closely related to the activity of the sex glands, enzyme 5-alpha reductase (5αR), and androgen receptor (AR) affect the hormonal activity of androgens. The cytochrome P450 (CYP450) plays an important role in the synthesis and breakdown of androgens. The overall results of this study show that the amount of factors studied) CYP450, 5αR, and AR) in diabetic people is significantly higher than in healthy people. These results suggest a link between these factors and the risk of diabetes and may explain the steroid hormonal changes in diabetic patients and therefore the different responses to treatment in patients with T2DM.

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None

## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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