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# Correlation between ABO blood groups with insulin resistance in type II diabetes mellitus patients using Metformin

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ABSTRACT

The aim of the present study to investigate the relationship between ABO blood group with glycaemic control and insulin resistance in type II DM using metformin therapy. Fifty-five patients newly diagnosed with type 2 diabetes mellitus collected in diabetic centre Al- Husseini hospital by the specialist physician according to the American Association of Diabetes, from December 2015 to May 2016. ABO blood group based on insulin resistance, blood glucose and body mass index were determined and correlated with each other. AB blood group had more reduction in FBG, HbA1c %, BMI (-38.6,-.22.8,-55.1, -4.3, respectively) by effect metformin treatment after three months from other blood groups. Correlation of ABO blood groups based on insulin resistance with FBG and HbA1c% showed AB blood group had more reduction in glycemic control (FBG, HbA1c %) after metformin treatment. The present study showed that different ABO blood groups had a different effect on glycemic control and insulin resistance about metformin treatment in newly diagnosed type 2 diabetes after three months. Also, AB blood group more association with response metformin treatment compared with other blood groups.

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## INTRODUCTION

Diabetes Mellitus (DM) recognized as a global significant public health problem, and diabetes is one of the main contributors to ill health and premature mortality worldwide (Bener and Yousafzai, 2014). DM is a common medical problem having significant morbidity and mortality. The total number of people with DM is projected to 366 million in 2030 (Shaw *et al.,* 2010). DM described as a modern epidemic which is emerging rapidly in developing countries. The etiology of DM is complicated, but factors such as genetic, immunological, and environmental are involved. Diabetes has a genetic predisposition, although environmental factors do play their role in its genetic expression. The primary human blood group system is ABO, and the incidence of ABO groups varies markedly in different races, ethnic groups, and socioeconomic groups in different parts of the world (Kaur *et al.,* 2016). All human populations share the same blood group systems, although they differ in the frequency of specific types (Kaur *et al.,* 2016).

Blood group antigens are hereditary determined and play a vital role in transfusion safety, understanding genetics, inheritance pattern, and disease susceptibility. The absence and presence of blood group antigens associated with various diseases. It was reported that there are multiple associations between particular ABO phenotypes and increased susceptibility to disease (Di Martino *et al.,* 2014). The relationship between the ABO/rhesus (Rh) blood groups and various diseases has generated a great deal of interest (Okon *et al.,* 2008). Certain diseases show a strong association with the ABO/Rh blood groups, notably peptic ulcer and gastric cancer (Zhang *et al.,* 2014). Several studies have investigated the possible relationship between type 2 diabetes mellitus and the ABO/ Rh blood groups (Jaffe *et al.,* 2016). The blood groups of diabetics have been extensively studied since McConnell's suggestion in 1955 of an increased frequency of blood group A among these patients (Green *et al.,* 2013). In Copenhagen, an excess of blood group O was found in male diabetics (Meo *et al.,* 2016). In Italy and Trinidad, results showed an increased frequency of blood group B among diabetics, but in Germany, Glasgow, Bangladesh (Jaggi and Yadav, 2014) and a number of other recent studies (Nemesure *et al.,* 2006), no association was apparent between type 2 diabetes mellitus and blood group in the people with diabetes studied. Recently, the relationship between ABO blood groups and disease susceptibility has generated a lot of interest. Thus the current study directed to discover the association between DM and ABO blood groups in the general population (Anstee, 2010).

Insulin resistances are a more common complaint in persons who are overweight or obese, added abdominal fat, and are not physical activeness. If beta cells of the pancreas can yield enough insulin, that regulates blood glucose level within the normal range. A dysfunction in insulin production caused by either beta cell dysfunction or persistence elevation in serum glucose will eventually lead to prediabetes or diabetes (Sumitani *et al.,* 2014).

Metformin has now been on the market for more than 50 years and established as the first-line agent of choice for the management of type 2 diabetes. In this context, the joint guidelines issued by the American Diabetes Association and the European Association for the Study of Diabetes strongly and repeatedly suggest that this agent should be used alongside lifestyle modification at diagnosis of type 2 diabetes (Nathan *et al.,* 2009).

The primary mechanisms include anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues (Ando *et al.,* 2014). Reduced appetite is a useful action of metformin, contributing to weight loss, which is beneficial, given that the vast majority of patients are obese. Diminished intestinal carbohydrate absorption plays a role in reducing postprandial hyperglycemia (Stephen *et al.,* 2014).

The study aimed to investigate the relationship between ABO blood groups and the effect of (metformin) on glycemic control and insulin resistance in newly diagnosed type 2 diabetes mellitus as first-line thereby.

## METHODS

### Subjects

This study designed as open-label prospective clinical trial carried out at Al Hussein Center for Diabetes and Endocrinology in Iraq, this study included 55 newly diagnosis type 2 diabetes mellitus. All patients must take metformin treatment (1500 mg) signal dose for three months.

Fifty-five patients assigned into four groups, according to blood groups (AB, B, A, O). All four groups receive metformin for three months; also, 32 subjects were the healthy control group.

This study approved by the ethical committee in Al Hussein centre for Diabetes and Endocrinology and Al- Mustansiriya College of pharmacy and written informed consent obtained from all participants.

### Anthropometry measurement

Measurement for each patient's height (cm), weight (kg) with a rigid stadiometer and calibrated scale (Seca 764, Seca Co., Ltd, Birmingham, United Kingdom). BMI was calculated as body weight (kg) divided by the square of height (m) (kg /$m^2$) (Ganz *et al.,* 2014).

### Blood sample collection

Venous blood samples were taken after a 12-h overnight fast. Fasting plasma glucose (FPG) (Gasparyan *et al.,* 2015), glycosylated hemoglobin (HbA1c) were assayed using the Cobs Integra 400 plus automatic biochemistry analysis system, measured using an enzymatic method. Blood type test by blood method agglutination, insulin was measured by monoclonal antibody-based sandwich enzyme-linked immunosorbent assay (ELISA) (Yin *et al.,* 2013). Insulin resistance index was calculated by homeostasis model assessment of insulin resistance (HOMA-IR) as (fasting insulin µIU/ml) × (fasting glucose mg/dl) / 405 (Sumitani *et al.,* 2014).

### Statistical analysis

Continuous data were tested using the Anderson Darling test to clarify if they follow a normal

**Table 1: Demographic Data and Baseline Characteristic of the Patients**

| Variables | | Control | Patients | P value |
|---|---|---|---|---|
| Number | | 32 | 55 | - |
| Age (years), mean ± SD | | 46.1 ± 9.7 | 46.9 ± 9.7 | 0.713 [NS] |
| BMI (kg/m$^2$), mean ± SD | | 25.3 ± 1.3 | 32.5 ± 4.6 | <0.001 [Sig.] |
| Gender, n (%) | Female | 11 (34.4%) | 20 (36.4%) | 0.852 [NS] |
| | Male | 21 (65.6%) | 35 (63.6%) | |

NS: non-significant, Sig.: significant difference
Independent t test, chi square test

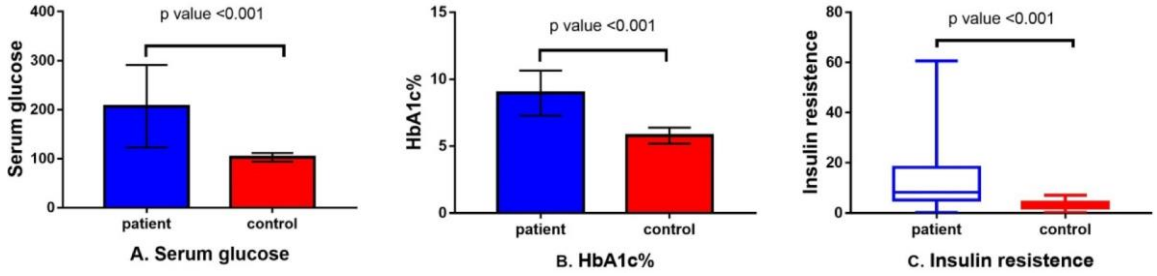


**Figure 1: Comparison between patients and control at baseline**

**Table 2: Effect of Treatment with metformin on Fasting Plasma Glucose (mg/dL) in Patients with Type 2 Diabetes after three months of Treatment with different blood groups**

| Variables | Patients (baseline) | Patients (after three months) | P value |
|---|---|---|---|
| All (n=55) | 206.9 ± 84.2 | 148.7 ± 43.0 | 0.027 [Sig.] |
| | Blood groups | | |
| A (16) | 192.3 ± 95.5 | 163.0 ± 58.4 | 0.207 [NS] |
| AB (12) | 210.3 ± 78.1 | 129.2 ± 22.4 | 0.008 [Sig.] |
| B (14) | 229.2 ± 110.4 | 149.6 ± 35.6 | 0.008 [Sig.] |
| O (13) | 197.5 ± 54.8 | 148.0 ± 39.4 | 0.001 [Sig.] |

NS: non-significant; Sig.: significant difference; Paired t-test

distribution (all variables except serum insulin and insulin resistance did not follow a normal distribution). Continuous data that follow normal distribution presented using there mean, and standard deviation, those that did not normal distribution presented using there median and interquartile range (IQR; 25% to 75% of the data). Paired t-test and independent t-test (between patients and control) were used (for normally distributed data). Mann Whitney U test to analyze the difference in the median between 2 groups (non- normally distributed data), if two paired groups Wilcoxon rank test used. Linear regression model used to analyze the correlation between 2 continuous variables; the correlation coefficient calculated which interpreted into two main outcomes: the sign (if the positive direct relationship, and negative mean inverse relationship), magnitude (<0.25 weak. 0.25 – 0.49 moderate, >0.5 strong correlation). All analysis performed using SPSS version 20.0 (Chicago, IL, USA), p-value considered significant in <0.05.

## RESULTS AND DISCUSSION

Demographic data and baseline characteristics of patient and subjects shown in table 1; only BMI significantly elevated in patients, FBS for patients is significantly higher compared control at baseline (see figure 1, A), the patient had a significant reduction in FBS from baseline to the end of the study (p-value = 0.027) as illustrated in table 2 (at baseline patients had significantly higher FBS compared to normal subjects). The blood groups (A, B, AB and O) after 3 months had significant reduction in serum FBG compared to baseline values (see table 2), in which blood group AB had more reduction in serum FBG from blood group B and blood group O (38.6%, 34.7%, and 25.1%; respectively), while blood group A had non-significant change (see figure 2)

HbA1c for patients is significantly higher at baseline compared with control (see figure 1, B), the patient had a significant reduction in HbA1c from baseline to the end of the study (p-value <0.001). All four groups had a significant reduction in HbA1c, and their effect was similar (p-value for interaction = 0.509, calculated using two way ANOVA) Where blood group AB more reduction in HbA1c than the rest blood groups as illustrated in table 3, figure 3.

Serum insulin was significantly higher in patients 15.9 (10.7 – 32.3) compared to control 13.5 (8.8 – 17.5) at baseline, and at the end of the study, the

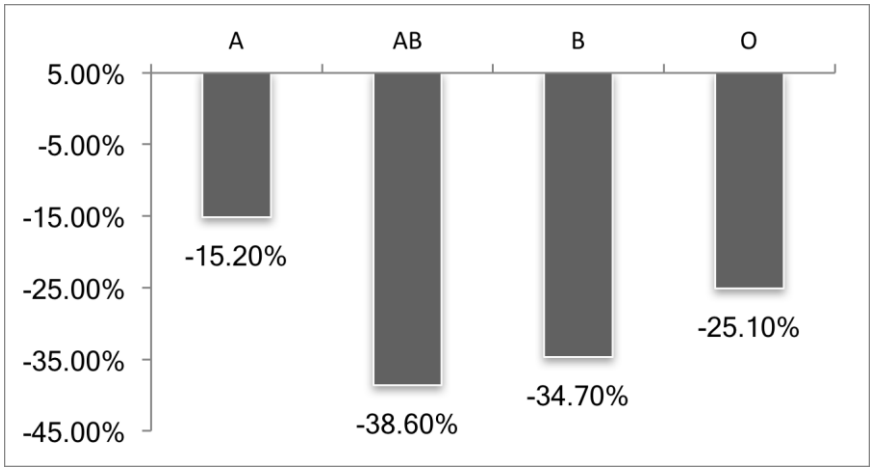


**Figure 2: Shown percentage reduction in Fasting blood glucose for each blood group**

**Table 3: Effect of Treatment with metformin on Glaciated Hemoglobin (HbA1c%) in Patients with Type 2 Diabetes after three months of Treatment with different blood group**

| Variables | Patients (baseline) | Patients (after three months) | P value |
|---|---|---|---|
| All (n=55) | 8.97 ± 1.68 | 7.43 ± 1.43 | <0.001 [Sig.] |
| | Blood groups | | |
| A (16) | 9.16 ± 1.83 | 7.50 ± 1.63 | <0.001 [Sig.] |
| AB (12) | 8.96 ± 2.07 | 6.92 ± 1.28 | 0.008 [Sig.] |
| B (14) | 8.46 ± 1.56 | 7.39 ± 1.05 | 0.018 [Sig.] |
| O (13) | 9.29 ± 1.23 | 7.89 ± 1.6 | 0.008 [Sig.] |

Sig.: significant difference; Paired t-test

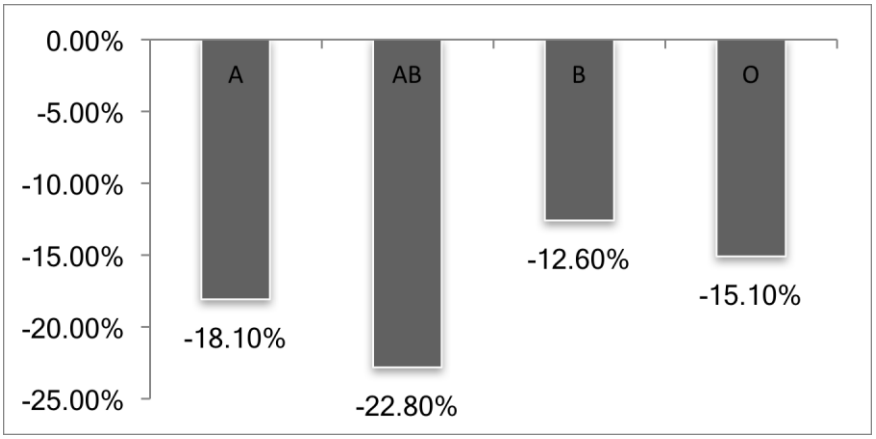


**Figure 3: Showing the percentage reduction in HbA1c in patients for each blood group**

reduction in serum insulin was not significant in patients 14.3 (9.9 – 24.4) as illustrated in figure 4.

Patients had significantly higher IR (insulin resistance) compared to control at baseline (see figure 1, C), on the other hand, IR significantly reduced in patients from baseline till the end of the study. Both (AB and O) blood groups in patients had significantly reduced IR, in which blood group AB more significant (p = 0.004) than blood group O (p = 0.046), while groups (A and B) did not reduce the IR significantly as illustrated in table 4, figure 5.

(AB, and A) blood group had significant reduction in BMI in patients newly diagnostic DM after three months of metformin treatment, while the rest (B, O) was not significant, as shown in table 5, figure 6.

AB blood group show the weakest correlation between FBS and IR which mean the reduction in FBS in this group are not dependent on IR, while blood groups like (O, A, and AB in ascending order) are more affected by insulin resistance (since there is clear linear relationship between IR and FBS, as illustrated in table 6.

AB blood shows the weakest correlation between HbA1c and IR which mean the reduction in HbA1c in this group are not dependent on IR. Only in blood group A HBA1c had a significant linear relationship with IR (indicating that HBA1c will be susceptible to change in IR in this group) as shown in table 7

The result of the present study indicated a significant reduction in FBG, HbA1c from baseline to the

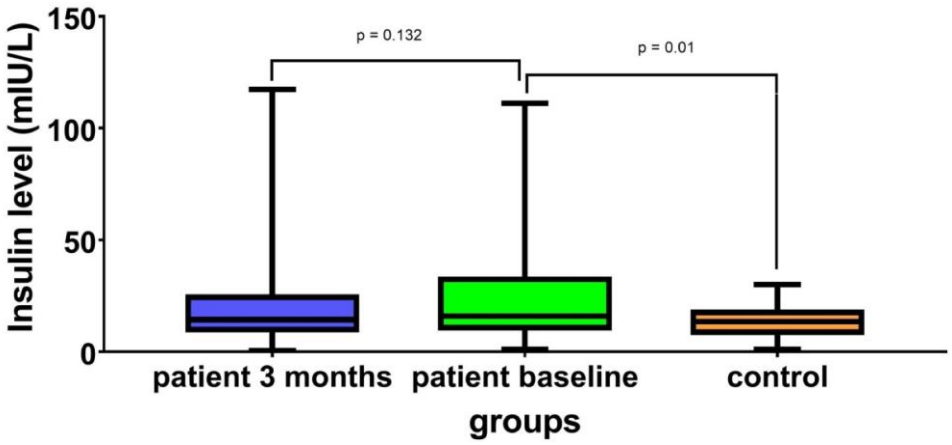


**Figure 4: Boxplot for the effect of Treatment with metformin on Insulin level (mIU/L) in Patients with Type 2 Diabetes after three months**

**Table 4: Effect of Treatment with metformin on Glaciated Hemoglobin (HbA1c%) in Patients with Type 2 Diabetes after three months of Treatment with different blood group**

| Variables | Patients (baseline) | Patients (after three months) | P value |
|---|---|---|---|
| All (n=55) | 8.3 (5.2 – 18.2) | 5.1 (3.2 – 8.3) | 0.002 [Sig.] |
| | Blood groups | | |
| A (16) | 5.8 (3.9 – 11.0) | 5.0 (3.3 – 9.8) | 0.737 [NS] |
| AB (12) | 11.8 (6.2 – 21.0) | 5.3 (2.7 – 6.9) | 0.004 [Sig.] |
| B (14) | 8.9 (6.8 – 35.4) | 6.0 (3.7 – 14.1) | 0.158 [NS] |
| O (13) | 8.7 (5.2 – 12.8) | 4.4 (2.9 – 7.5) | 0.046 [Sig.] |

NS: non-significant, Sig.: significant difference; Wilcoxon rank test

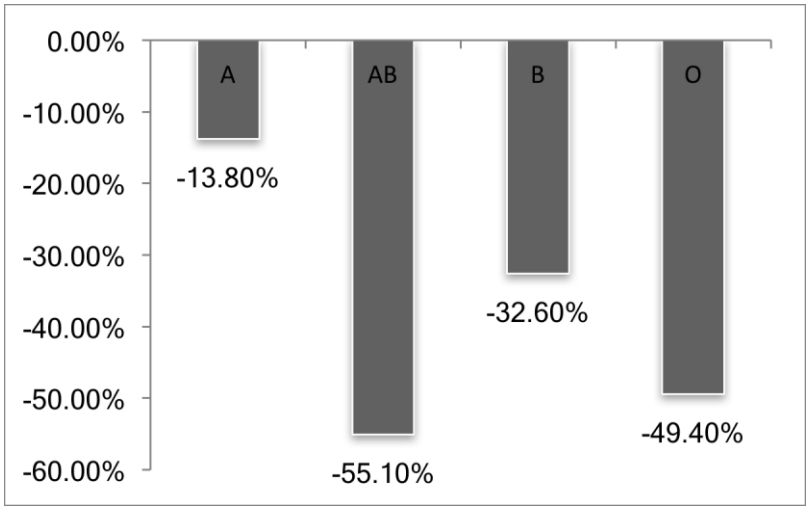


**Figure 5: Showing the percentage reduction in insulin resistance in patients for each blood group**

end of the study. Treatment with metformin in a dose of 1500 mg per day reduces the HbA1c level by (1-2%) and reduce FBG levels by 60 to 80 mg/dL after three months of therapy. These results agree with other studies. (Bennett *et al.,* 2011) In Go-Darts study they reported that genetic variation altered glycemic control response to metformin, where the ataxia telangiectasia mutated (ATM) gene, attenuated the phosphorylation and activation AMAK in response to metformin (Liu *et al.,* 2016). The variant of the OCT1 gene and variant of MATE1 gene have both been shown to enhance the reduction of HbA1c in response to metformin (Becker *et al.,* 2009). Zhou et al. showed an association between large loci in chromosome 11 that altered glycemic control response to metformin (Zhou *et al.,* 2015).

Insulin resistance, high insulin level in the body (hyperinsulinemia) and impaired insulin action are risk factors for type 2 DM and polycystic ovary syndrome (Sharma *et al.,* 2014). In the present study results a significant reduction in the value of insulin resistance when compared to patients treated with metformin-treated for three months, these results agree with a previous study (Gupta *et al.,* 2009). Metformin therapy in polycystic ovary

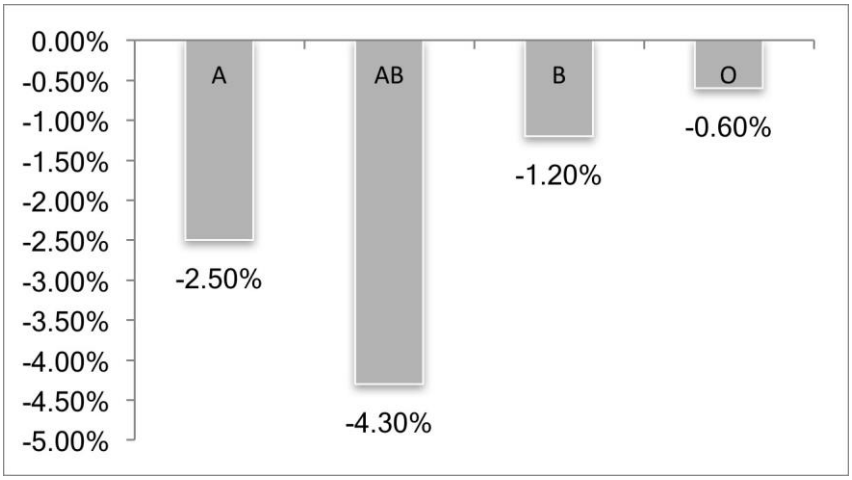


**Figure 6: The percentage reduction in BMI in patients for each blood group**

**Table 5: Effect of Treatment with metformin on BMI in Patients with Type 2 Diabetes with different Blood group after three months**

| Variables | Patients (baseline) | Patients (after three months) | P value |
|---|---|---|---|
| A (16) | 31.4 ± 5.1 | 30.6 ± 5.2 | <0.001 [Sig.] |
| AB (12) | 34.5 ± 4.3 | 33.0 ± 4.9 | 0.021 [Sig.] |
| B (14) | 32.6 ± 4.2 | 32.2 ± 4.1 | 0.242 [NS] |
| O (13) | 31.7 ± 4.6 | 31.5 ± 4.6 | 0.583 [NS] |

NS: non-significant, Sig.: significant difference; Paired t-test

**Table 6: Correlation between FBG and Insulin resistance for each blood group in patients after three months of therapy**

| Blood groups | Pearson correlation coefficient | P value |
|---|---|---|
| A | 0.481 | 0.059 [Sig ] |
| AB | 0.288 | 0.364 [NS] |
| B | 0.830 | <0.001 [Sig] |
| O | 0.424 | 0.149 [NS] |

Linear regression analysis

**Table 7: Correlation between HbA1c and Insulin resistance for each blood group in patients after three months of therapy**

| Blood groups | Pearson correlation coefficient | P value |
|---|---|---|
| A | 0.682 | 0.004 [SIG] |
| AB | -0.017 | 0.959 [NG ] |
| B | 0.228 | 0.434 [NG] |
| O | 0.398 | 0.179 [NG ] |

Linear regression analysis

syndrome reduces hyperinsulinemia, insulin resistance. Metformin is associated with short-term weight loss, improvement of insulin sensitivity, and decreased visceral fat (Grønbæk *et al.,* 2012). The ataxia telangiectasia mutated (ATM) gene, was supposed as the most likely candidate given its association with insulin resistance and T2D (Huang and Florez, 2011).

In the present study, both (AB and O) blood group had significantly reduced the value of insulin resistance, while the rest was insignificant, suggesting the association between ABO blood group (AB, O) genes with ataxia telangiectasia mutated (ATM) gene in treatment T2D with metformin. We theorized that this relationship in the present study is the first related to the blood group (AB, O) gene with metformin in reducing insulin resistance. In AB blood group since in our results revealed no correlation between HBS or HBA1c against insulin resistance, suggesting that AB blood group is less sensitive to insulin resistance in one hand and had better ability to reduce both insulin resistance and obesity (evidenced by lowering BMI significantly) on the other hand which point us to understand the better response in AB blood group in terms of glycemic control, O blood group had similar effect to AB blood groups but was lower in magnitude, we speculate it caused by lower ability (statistically insignificant) reduction of BMI after 3 months of therapy with metformin while patients with blood group O reduce insulin resistance significantly in was lower than that of AB blood group (Esposito *et*

*al.,* 2012), all these different responses in glycemic parameters lead us to think a different genetic variations in the ABO gene cause possibly different outcomes when using metformin therapy.

## CONCLUSION

The results of this establish a relationship between the ABO gene and molecular mechanism action of metformin. Its further confirms that blood group AB was more related to metformin effect compared with other ABO blood group system. The genetic role plays an important role in response to treatment of metformin and differentiation between blood groups. This study considers the novel hypoglycemic action of metformin on blood groups which may explain in part the apparent effect on glycemic control markers (FBG, HbA1c, and Insulin resistance).

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## Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kadhim, Rahmah and Fawzi they have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: Kadhim, Mohammed, Hussein and Fawzi. Acquisition of data: Mohammed, Alkutubi, Khalaf and Kadhim. Analysis and interpretation of data: Mohammed and Fawzi.

## Conflict of Interest

The authors declare that they have no conflict of interest

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