

## Gender and Therapy Influence the Role of Metformin in Manage Type 2 Diabetes: The Role of OCT2

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### Abstract:

**Background:** Response to metformin varies among T2DM patients. The influence of gender, therapy type, and renal excretion the organic cation transporter 2 (OCT2) remains incompletely understood.

**Objectives:** To evaluate the impact of gender and type anti-diabetic therapy metformin efficacy, while also investigate the role of organic cation transporter (OCT2) in renal excretion and clinical outcomes.

**Methods:** A total of 60 T2DM case and 26 healthy individuals matched for age and sex (aged 30-65 years). After 8-12 hours of fasting, Biochemical and Hormonal analyses were carried out on blood sample, assessing HbA1c, insulin, C-peptide, glucagon, and OCT2 concentrations using ELISA and HPLC techniques. Statistical testing was performed using independent t-test and ANOVA, applying a significant threshold of  $p < 0.05$ .

**Results :** Combination therapy with metformin and other anti-diabetic drugs did not provide additional glycemetic benefit compared with metformin monotherapy. In the majority of parameters, no significant different for most parameters, except for higher glucagon levels in female patients. Finding support a mechanistic contribution of OCT2 variability to differences in metformin response.

**Conclusions:** In this cohort, combination therapy did not improve glycemetic outcomes beyond metformin monotherapy, emphasizing the need for personalized treatment. Consideration of gender and OCT2-related variability may optimize therapeutic decisions and improve long-term outcomes.

**Keyword:** Metformin, Type 2 Diabetic Mellitus, Gender, Organic Cation Transporter (OCT2), Insulin Resistance.

**Note:** The research is based on a master's thesis.

### Introduction:

T2DM is a persistent endocrine disorder signified by IR (Insulin Resistance) plus hyperglycemia resulting from pancreatic beta cell disorder and reduced peripheral glucose utilization (Ismail ZM et al., 2020; Al-Kuraishy HM et al., 2024). T2DM accounts for 90% of diabetes cases and primarily affects individuals over 40 years (Janssen JA et al., 2021). It's strongly associated with vascular complications, including cardiovascular disease and diabetic kidney disease, contributing to increased morbidity and mortality (Galicia-Garcia U et al., 2020). Metformin act as considered the first- line pharmacological for T2DM, this treatment boosts insulin sensitivity and decreases hepatic glucose production through several mechanisms such as activating AMP-activated protein kinase, enhancing lipid metabolism, and lowering glucose levels (Salman AN et al., 2023; LaMoia et al., 2021). Despite its wide use effectiveness, the mechanisms of metformin action are complex, and variability in patient response continues to be observed. OCT2 plays a central role in the renal excretion of metformin as well as partly explains interindividual differences in drug response (Borra et al., 2023). However, the influence of other factors \_ particularly gender, hormonal differences, and the type of anti-diabetic therapy \_remains in completely understood. It is essential to have a deeper understanding of these variables for developing more personalized therapeutic approaches and improving long-term outcomes in T2DM patients.

### Literature Reviews:

#### 1-Hakim et al. (2022)

. **Title:** Glycemic Response to Metformin and Its Association with Age and Gender in Type II Diabetes.

.**Summary:** The study shows how gender influence the glycemic response to metformin in T2DM.the finding indicated that sex does not effect on the response. This agrees with our results which no significant difference in response observed between female and male.

#### 2- Arne et al. (2024)

**Title:** Sex differences in adipose insulin resistance are linked to obesity, lipolysis and insulin receptor substrate 1

**Summary:** who contend that insulin resistance is comparable between men and woman , rather manifests primarily in the context of obesity, the lack of significant differences in fasting insulin levels and HOMA-IR further supports the conclusion that insulin resistance is not expressed differently between genders in this sample.

### 3- Huang et al. (2024)

**Title:** Sex differences in the plasma glucagon responses to a high carbohydrate meal and a glucose drink in type 2 diabetes.

**Summary:** Reviews indicate that male contacts have noticeably higher glucagon levels, which leads to hyperglycemia, The higher baseline glucagon levels observed in female in our result and that may reflect altered alpha – cell function or regulatory mechanism, which could underlie these sex specific .This highlights the necessity of individualized treatment plans that take sex into account.

### 4-Aloufi et al. (2023)

**Title:** Efficacy of metformin monotherapy in newly diagnosed type 2 diabetes mellitus patients treated at Prince Mohammed Bin Abdulaziz hospital, Riyadh, Saudi Arabia

**Summary:** observed that metformin alone was successful in establishing management of blood glucose levels in individuals with newly diagnosed type 2 diabetes and illustrated that metformin monotherapy considerably improved glycemic outcomes without the immediate requirement for additional medicines. This Aligns with our result in which no difference observed in glucose management when used other anti-diabetic drug with metformin.

#### **Study Objective:**

The principal objective of this study is to examine how factors such as gender, and type of anti-diabetic therapy influence the therapeutic impact of metformin in treating Type2 diabetes (T2DM), along with exploring the role of OCT2 transport in the biguanide drug renal excretion.

#### **Methodology:**

The current cross – sectional study that included 86 participates, consisting of 60 individuals diagnosed with Type 2Diabetes Mellitus (T2DM) and 26 healthy controls matched for age and gender. The participants were aged between 30 and 65 years. Based on the American Diabetes Association guideline's , the diagnosis of T2DM was confirmed (ADA,2024). A cases – control study design was applied over six-month period, from September to February, at the Specialized Center for Endocrinology and Diabetes in Baghdad, Iraq.

#### **Inclusion Criteria:**

Patients diagnosis with T2DM for at least 3 months and receiving metformin therapy.

### Exclusion Criteria :

Individuals with Type 1 Diabetes Mellitus, hypersensitivity to biguanides, pregnancy, insulin therapy, active malignancy, use of nephrotoxic medications , severe cardiovascular conditions , liver cirrhosis , or anemia.

### Data collection:

Venous samples (5mL) was obtained for each participant post – overnight fasting lasting 8-12 hours. The blood was collected from the antecubital vein using sterile syringes and divided into two tubes: one EDTA tube for HbA1c analysis and one plain tube for serum separation, to measure other parameters. After clotting at room temperature, the samples were centrifugated at 3000 rpm for 10 min. The serum was separated into aliquots and stored at -20 C for future analysis.

### Biochemical Analysis:

. **High -performance liquid chromatography** was used to measure HbA1c levels

.FBS, insulin, C-peptide, glucagon, and OCT2 concentrations enzyme – linked immunosorbent assay kits were used to assess the levels, following the manufactures instructions:

.FBS kit\ Solar Bio\ China.

. fine test ELSIA Kit for human \ C-peptide \China.

.Human GC(Glucagon), Human INS(Insulin), and Human Organic Cation Transporter2 (OCT2) ELISA Kit.

### Statistical analysis

For stational analysis ,IBM SPSS version 28.0. (IBM corp., Armonk, NY, USA) was used. The Kolmogorov -Simirnov test was employed to examine the normality of the data. Continuous variables with a normal distribution are presented as the mean $\pm$  standard deviation (SD), while frequencies and percentages were applied to the categorical variables. The independent t-test was conducted to compare two distinct groups. After evaluating differences across studies group categories using a one-way ANOVA, pairwise differences were found by performing Tukey's post-hoc test. The connections between categorical variables were evaluated using the chi-square test. For investigating an association across continuous parameters including HbA1c, HOMA-IR, glucagon, and OCT2 levels, Pearson correlation analysis was used. A p- value smaller than 0.05, indicating stational significance.

### Ethical Considerations

Approval for the study was granted by the ethics committee of Al-Mustansiriyyah University, Baghdad, Iraq (Approval No.: BCSMU/9240/0054Z). All participants provided written informed consent. A structured questionnaire are utilized to receive demographic and lifestyle data (including age, gender, medical history, social status, height, BMI, lifestyle, blood pressure, treatment duration, therapeutic dose, and side effects), without recording any personal information.

### Results:

#### 1-Clinical and Demographic Features of the Study Participants

**Table (1): The Demographic Characteristics of T2DM case group and the Apparently Healthy Group.**

Parameter		Patients (n=60)	Controls (n=26)	P-value
Age group	≤ 40	7 (11.67%)	5 (19.23%)	0.498
	>40	53 (88.33%)	21 (80.77%)	0.498
Sex	Male	29 (48.34%)	12 (48.48%)	0.116
	Female	31 (51.66%)	14(51.52%)	0.199
Marital status	Single	3 (5 %)	3 (11.54%)	1.0
	Married	57 (95%)	23 (88.46%)	0.668
Duration of diabetes (years)	≤ 5	24 (40%)		
	>5	36 (60%)		
Duration of Antidiabetics use (years)	≤ 2	18 (30%)		
	>2	42 (70%)		
Metformin Dose (mg/day)	Low dose (500 mg)	53 (88.33%)		
	High dose (1000 mg)	7 (11.67%)		
Type of Antidiabetic Therapy	Metformin only	25 (41.67 %)		
	Metformin+ another antidiabetic drug	35 (58.33%)		
Family history	Yes	4 (6.67%)		
	No	56 (93.33%)		

## 2-Gender Differences in Metabolic Indicators and Regulation of Blood Glucose in T2DM cases

Table (2): The Metabolic and Glycemic Parameters Associated with Gender in T2DM patients

Parameter	Patients Woman (n= 31)	Patients Man (n= 29)	P-value	statistically significant
FBG (mg/dl)	311.23 ± 96.71	302.196 ± 80.67	0.69	[NS]
HbA1c% (Before)	10.66 ± 2.17%	10.64 ± 2.08%	0.97	[NS]
HbA1c % (After)	10.49 ± 2.33%	10.53 ± 2.00%	0.94	[NS]
Fasting Insulin (µIU/mL)	22.12 ± 1.61	22.81 ± 1.67	0.10	[NS]
HOMA-IR	5.42 ± 1.79	5.58 ± 1.65	0.71	[NS]
HOMA-BCF	36.72 ± 13.66	37.84 ± 13.25	0.74	[NS]

## 3-Sex Differences in C-Peptide, Glucagon, and OCT2 Levels Among T2DM Table (3): Comparison among C-Peptide, Glucagon, and OCT2 Levels Among T2DM Affiliated to Gender

Parameter	Patients Woman (n= 31)	Patients Man (n= 29)	P- value	statistically significant
C-peptide(ng/mL)	1.58 ± 1.13	2.38 ± 2.28	0.08	[NS]
Glucagon(pg./mL)	215.28 ± 61.19	166.37 ± 69.49	0.007 *	[S]
OCT2(pg./mL)	140.19 ± 52.88	130.61 ± 46.67	0.45	[NS]

## 4- Comparison of Biochemical, Physiological, and Hormonal Parameters Between Metformin Monotherapy and Combination Therapy in Diabetic Patients.

**Table (4): Comparison of Biochemical, Physiological, and Hormonal Parameters in T2DM cases Received Metformin Monotherapy versus Combination Therapy**

Parameter	Metformin Only n=25 (41.67%) (Mean ± SD)	Metformin + Other Antidiabetic Drugs n=35 (58.33%) (Mean ± SD)	P value	Statistically significant
FBG (mg/dl)	303.69 ± 86.19	309.12 ± 91.61	0.817	[NS]
HbA1c % (Before)	10.61% ± 0.019	11 % ± 0.02	0.89	[NS]
HbA1c % (After)	10.33 ± 2.06	10.59 % ± 2.25	0.566	[NS]
Fasting Insulin (μU/mL)	22.48 ± 1.84	22.43 ± 1.55	0.909	[NS]
HOMA-IR	5.42 ± 1.74	5.56 ± 1.72	0.758	[NS]
HOMA-BCF	44.63 ± 31.39	35.95 ± 12.28	0.142	[NS]
C-peptide (ng/mL)	2.11 ± 1.86	1.87 ± 1.79	0.617	[NS]
Glucagon (pg./mL)	210.60 ± 76.49	178.10 ± 61.24	0.073	[NS]
OCT2 (pg./mL)	146.03 ± 54.78	128.07 ± 45.22	0.170	[NS]

#### Discussion:

As presented in Table (1), Age, Se, and marital status, as demographic variables, did not show any significant difference between the case and controls. The lack of significant baseline variation enhances the validity of sub sequent group comparison, minimizing the potential for confounding due to demographic imbalance. Notably, 88.3% of patients, whether on metformin alone or in combination with other agents, was given a low dose 500 mg/ day of metformin tables. Nearly all had a disease duration exceeding two years and had been on antidiabetic treatment for more than two years. These observations align with the American Diabetes Association (ADA, 2024) guidelines, which continue to recommend metformin- particularly the extended -release formulation\_ as the cornerstone of therapy, given its proven cardiovascular safety, glycemic efficacy, and favorable weight profile. The relatively high proportion of patients on combination therapy may reflect the progressive nature of T2DM and the eventual need for treatment intensification.

Family history of diabetes was documented in only 6.7% of patients, a finding that contrasts with epidemiological evidence showing that genetic predisposition substantially increases diabetes risk. For example, a family history has been associated with fourfold increase in diabetes prevalence in the population of United States (Sacks et al., 2017) and, in extreme cases, with up to a twelvefold increase in risk (Ahmed et al., 2024; De Pergola et al., 2021). Similarly, Ramezankhani et al. (2022) demonstrated that family history, combined with obesity, markedly elevated lifetime risk of diabetes in Iranian cohort. The low frequency observed here may point to underreporting or suggest that lifestyle and environmental conditions (Such as diet and insufficient physical inactivity) play a more prominent role in the population. Turning to Table 2 and 3, There were no significant variations between male and female patients in fasting blood sugar, HbA1c, fasting insulin, or insulin resistance, or HOMA- $\beta$  cell function (HOMA -BCF). These findings suggest that gender did not significantly influence glycemic control, insulin resistance, or  $\beta$ -cell activity in this cohort. This result is consistent with evidence that metabolic outcomes in T2DM are broadly similar across sexes, despite reports of sex-specific differences in pathogenesis linked to hormonal or body composition factors (MacGregor et al., 2025). Arner et al. (2024) similarly informed that obesity, supporting absence the significant gender effects observed here.

Although no major sex-based differences in standard glycemic parameters were detected literature suggests that physiological, behavioral, and psychosocial factors may contribute to subtle sex differences in disease course (Estoppeya et al., 2023). For example, woman may present higher visceral adiposity and cardiovascular risk factors (de Ritter et al., 2023), and hormonal fluctuations related to pregnancy or menopause can worsen metabolic control (Kautzky-Willer et al., 2023). These nuances may not be fully captured by conventional measures such as FBG or HOMA-IR. In our study, C-peptide levels were slightly higher in males, although not statistically significant, consistent with prior reports linking testosterone to  $\beta$ -cell function (Zietz et al., 2000). Conversely, glucagon levels were significantly higher in females ( $p=0.005$ ), highlighting sex differences in  $\alpha$ -cell regulation. This matches reports by Huang et al. (2024) and Johson et al. (2023) emphasizing that hormonal and metabolic responses differ between sexes, reinforcing the need for individualized treatment approaches.

With respect to OCT2 expression, no notable contrasts were observed between both gender patients. Prior studies, however, have shown that diabetes can downregulate OCT2 expression via both genetic and epigenetics mechanisms (Grover et al., 2004; Galiero et al., 2023). Experimental data further indicate that androgen may enhance OCT2 expression, whereas estrogen exerts little influence (Ai et al., 2015). Schorn et al., (2021) additionally reported that high glucose concentrations can directly upregulate OCT2 in pancreatic tissue. These findings suggest that OCT2 regulation is complex and influenced by multiple biological factors beyond sex alone.

As shown in Table (4) indicates that there were no statistically significant differences between patients treated with metformin monotherapy and those on combination therapy with respect to glycemic or OCT2. These results imply that the addition of other antidiabetic drugs did not provide further benefit in this cohort. The finding is consistent with Lewis et al. (2024), who confirmed metformin's robust capacity to control fasting glucose independently. Likewise, Aloufi et al. (2023) demonstrated the effectiveness of metformin monotherapy in patients with newly diagnosed diabetes, with no immediate need for additional agents.

Nonetheless, evidence on combination therapy remains mixed. Tomlinson et al. (2022) reported improved glycemic outcomes with add-on therapy in patients with advanced insulin resistance, while Ji et al. (2021) and Ly et al. (2020) observed greater metabolic benefits when combination therapy was initiated early. These conflicting results underscore the importance of tailoring treatment to patient-specific factors such as insulin resistance, disease duration, and  $\beta$ -cell reserve. In our study, the absence of significant HbA1c differences between therapy groups suggests that for many patients, metformin alone may be sufficient, particularly in earlier disease stages or when  $\beta$ -cell function is preserved.

Overall, the present findings confirm three major points : (1) baseline demographic factors and family history had limited influence on clinical outcomes , likely reflecting environmental and treatment – related determine ; (2) gender did not significantly affect glycemic outcomes , through differences in glucagon regulation and hormonal influences highlight the need for sex -aware management ; and (3) combination therapy did not offer added benefits over metformin alone in this cohort, underscoring the importance of personalized therapeutic strategies in T2DM management

### Conclusions:

This study demonstrated that demographic factors , including age, sex , and material status , no significant variation was observed between patient and health group , thereby minimizing the risk of confounding in clinical comparisons. Family history of diabetes was reported at a relatively low frequency, suggesting that lifestyle and environmental determinants may play a more prominent role in this population. No significant sex- based differences were observed in fasting glucose, HbA1c, insulin resistance, or  $\beta$ - cell function. However, higher glucagon levels in females underscore sex-related variability in metabolic regulation. OCT2 expression did not differ significantly between males and females, through evidence from prior studies suggests its regulation in multifactorial, involving hormonal, genetic, and epigenetic mechanisms,

Importantly, combination therapy with metformin and other antidiabetic agents did not provide additional benefit compared with metformin monotherapy. These outcomes emphasize the significance of personalized medicine, reflect on issues such as sex-related hormonal influences, OCT2 variability, disease duration, and  $\beta$  -cell reserve when selecting therapeutic strategies for patients with T2DM.

### Recommendations:

**.Personalized Treatment:** Tailor diabetes treatment based on Age, gender, disease duration to improve glycemic control.

**.Study Hormonal Impact:** Further research on the role of sex hormones in glucose regulation and treatment response.

**. Long-term Studies:** Conduct studies on the effect of metformin alone versus combination therapy over time.

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تأثير الجنس والعلاج على دور الميتفورمين في إدارة مرض السكري من النوع 2: دور OCT2

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مستخلص البحث:

**الخلفية:** تختلف الاستجابة للميتفورمين بين مرضى سكر من مرضى السكري من النوع الثاني (T2DM) و مازال تأثير الجنس و نوع العلاج و الافراز الكلوي بواسطة الناقل الكيتوني العضوي (OCT2) غير محدد بدقة.

**الأهداف:** تقييم تأثير الجنس و نوع العلاج على فعالية الميتفورمين، و استقصاء دور OCT2 في الافراز الكلوي و تأثيراته السريرية.

**المنهجية:** شملت الدراسة 60 مريضا بالسكري من النوع الثاني و 26 شخصا سليما كمجموعه ضابطة، تراوحت أعمارهم بين 30-65 سنة. بعد 8-12 ساعة من الصيام. تم جمع عينات الدم الوريدية للتحليل الكيميائي الحيوي و الهرموني. تم تقييم تركيزات السكر الصائم، السكر التراكمي، الانسولين، الببتيد C الجلوكاجون و OCT2 باستخدام تقنيه ELISA & HPLC. أجريت التحليلات الإحصائية باستخدام اختبار ANOVA & t-test مع عتبه معتمد بها من  $P < 0.05$ .

**النتائج:** لم يظهر الجمع بين الميتفورمين و أدوية مضاد للسكري أخرى تحسنا إضافيا في السيطرة على الغلوكوز مقارنة بالميتفورمين وحده. كما لم تسجل فروق واضحة بين الجنسين في معظم المؤشرات، باستثناء ارتفاع مستوى الجلوكاجون بشكل ملحوظ عند الاناث المصابات بالسكري. دعمت النتائج مساهمة OCT2 في التباين الفردي في الاستجابة الدوائية.

**الاستنتاجات:** لم يحقق العلاج المركب ميزة إضافية مقارنة بالعلاج الأحادي بالميتفورمين، مما يؤكد أهمية التوجه نحو العلاج الشخصي. أخذ التباين المرتبط بالجنس و OCT2 قد يساعد على تحسين القرارات العلاجية و النتائج طويلة الأمد.

**الكلمات المفتاحية:** الميتفورمين، السكري من النوع الثاني، الجنس، ناقل الكيتوني العضوي، مقاومة الانسولين.