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Original article

The Impact of Metformin Therapy on Liver and Kidney Function in Type 2 Diabetic Patients: A Comparative Study Between Men and Women in Al-Bayda City

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This study examines the impact of metformin therapy on fasting blood sugar (FBS), renal function (urea and creatinine), and liver function (GOT, GPT, and ALP) in male and female type 2 diabetic patients. FBS levels, while numerically lower in females (106.8 ± 9.7 mg/dL) compared to males (119.7 ± 19 mg/dL), showed no statistically significant difference (p = 0.561), suggesting similar glycemic control across genders. Renal function assessment revealed significantly higher urea levels in males (37.40 ± 9.91 mg/dL) than in females (29.37 ± 5.02 mg/dL, p = 0.041), potentially indicating subtle gender-specific differences in renal function or protein metabolism. Similarly, creatinine levels were significantly higher in males (0.950 ± 0.158 mg/dL) compared to females (0.73 ± 0.1636 mg/dL, p=0.007), suggesting the need for closer renal monitoring in male patients. Liver function parameters, including GOT, GPT, and ALP, revealed no statistically significant differences between genders. Although males exhibited higher mean values of GOT (40.0 ± 74.2 U/L) and GPT (31.0 ± 18.05 U/L) compared to females (20.3 ± 8.60 U/L and 18.37 ± 8.77 U/L, respectively), the differences did not reach significance (p = 0.415 and p = 0.062). ALP levels were nearly identical between genders (p = 0.696), indicating no gender-based variations in biliary or bone metabolism. In conclusion, metformin therapy demonstrates comparable efficacy and safety in managing glycemic and hepatic parameters in both genders. However, higher renal biomarkers in males highlight the importance of gender-specific monitoring. Further studies are recommended to explore these trends with larger cohorts.

Introduction

Metformin, a biguanide derivative, is widely recognized as the first-line pharmacological therapy for type 2 diabetes mellitus (T2DM) [1]. It primarily functions by inhibiting hepatic gluconeogenesis, enhancing peripheral glucose uptake, and improving insulin sensitivity, thus reducing blood glucose levels without causing significant hypoglycemia [2]. The drug's mechanism involves the activation of AMP-activated protein kinase (AMPK), a crucial cellular energy sensor, which subsequently suppresses hepatic glucose production and promotes lipid oxidation [3]. Beyond glycemic control, metformin exhibits a range of pleiotropic effects that have attracted interest in fields such as oncology, cardiovascular research, and aging studies [4]. Emerging evidence suggests that metformin possesses anti-inflammatory, antioxidant, and anti-proliferative properties, which may contribute to its protective roles beyond diabetes management [5]. These effects are partly attributed to its ability to modulate mitochondrial function, decrease reactive oxygen species (ROS) production, and improve cellular stress response [6]. Recent studies have expanded the potential therapeutic applications of metformin to include renal protection, modulation of lipid profiles, and reduction of oxidative stress in various pathological models [7]. In models of nephrotoxicity, metformin has demonstrated the ability to attenuate oxidative damage, modulate inflammatory cytokine expression, and preserve renal histopathology, indicating its value as a protective agent beyond glucose regulation [8]. Millions of people worldwide suffer from type 2 diabetes mellitus (T2DM), a chronic metabolic disease marked by insulin resistance and poor glucose metabolism. Metformin, a biguanide that reduces blood glucose levels by blocking hepatic gluconeogenesis and enhancing peripheral insulin sensitivity, is one of the most often recommended medications for type 2 diabetes. Although the effectiveness of metformin in glycemic control is well established, research on the drug's effects on liver and renal function is still ongoing, particularly in populations with predisposed diseases like diabetes [9].

The liver plays a crucial role in glucose homeostasis and drug metabolism, making it a primary organ affected by metformin therapy. Studies have indicated that metformin might offer hepatoprotective effects

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in non-alcoholic fatty liver disease; however, concerns about lactic acidosis and its implications for liver function in diabetic patients necessitate further investigation. These effects may vary between genders due to differences in hormonal regulation and liver enzyme activity [10]. Similarly, the kidneys are central to metformin clearance from the body, and any impairment in renal function could exacerbate the drug's accumulation, increasing the risk of adverse effects such as lactic acidosis. Research has highlighted variations in kidney function between men and women, which may influence the pharmacokinetics of metformin. Understanding these differences is essential to optimize therapy and minimize risks [11]. In Al-Bayda City, where the prevalence of diabetes is rising, evaluating the effects of metformin on liver and kidney function among male and female patients is crucial for tailoring treatment approaches [12]. This study aims to explore these gender-based differences, providing insights into safer and more effective use of metformin in managing T2DM in this specific population.

Methods

This study was conducted in Al-Bayda City, targeting type 2 diabetic patients undergoing metformin therapy. The study population included male and female patients aged 30–70 years who had been on metformin treatment for at least six months. Participants were recruited from local clinics and hospitals, and inclusion criteria were established to ensure homogeneity in disease duration and dosage of metformin. Patients with pre-existing liver or kidney disease, alcohol abuse, or concurrent use of hepatotoxic or nephrotoxic drugs were excluded. The study employed a cross-sectional design to compare liver and kidney function parameters between male and female patients.

Blood samples were collected after fasting for 8–12 hours to measure biochemical markers of liver function, including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), as well as kidney function markers such as creatinine and urea. These tests were conducted using standardized enzymatic methods on an automated biochemical analyzer.

When appropriate, statistical analysis was performed using Graph Prism Pad and Minitab software (version 17). After detecting a normal distribution in the data and selecting a $P < 0.05$ threshold for significance, ANOVA analysis with the Tukey multiple comparison test was used to determine statistical significance.

Results

Comparison of fasting blood sugar between *Males and Females.*

The data presented in Table 1 compares fasting blood sugar (FBS) levels between male and female type 2 diabetic patients undergoing metformin therapy. The mean fasting blood sugar for males was 119.7 ± 19 mg/dL, while for females, it was 106.8 ± 9.7 mg/dL. Despite a numerically lower mean FBS in females compared to males, the difference was not statistically significant, as indicated by a p-value of 0.561.

Table 1.Comparison of fasting blood sugar Between Males and females

Items	Males Mean± SD (n=10)	Females Mean± SD (n=10)	P-value
FBS	119.7±.19	106.8 ±9.7	0.561

Comparison of Urea and Creatinine Between Males and Females

Table 2 presents a comparison of urea and creatinine levels between male and female type 2 diabetic patients undergoing metformin therapy. Urea Levels: The mean urea level in males was 37.40 ± 9.91 mg/dL, while in females, it was significantly lower at 29.37 ± 5.02 mg/dL. The difference in urea levels was statistically significant, with a p-value of 0.041. Creatinine Levels: Similarly, creatinine levels were higher in males (0.950 ± 0.158 mg/dL) compared to females (0.73 ± 0.1636 mg/dL), with a highly significant p-value of 0.007. The higher creatinine levels in males are likely due to greater muscle mass, as creatinine is a byproduct of muscle metabolism.

Table 2.Comparison of Urea and Creatinine Between Males and Females.

Items 'Mean± SD'	Male	Female	P-Value
Urea (mg/dl)	37.40 ±9.91	29.37±5.02	0.041
creatinine (mg/dl)	0.950 ±0.158	0.73 ±0.1636	0.007

Comparison of liver function tests between males and females

Table 3 compares liver function test parameters (GOT, GPT, and ALP) between male and female type 2

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diabetic patients undergoing metformin therapy. GOT (Aspartate Aminotransferase): The mean GOT levels in males were 40.0 ± 74.2 U/L, compared to 20.3 ± 8.60 U/L in females. Despite the higher mean value in males, the difference was not statistically significant (p-value 0.415). GPT (Alanine Aminotransferase): The mean GPT levels were also higher in males (31.0 ± 18.05 U/L) compared to females (18.37 ± 8.77 U/L), with a p-value of 0.062, approaching but not reaching statistical significance. While this difference might indicate a trend toward higher hepatic enzyme activity in males, it may not be clinically meaningful. Factors such as muscle mass, metabolic rates, or slight variations in drug metabolism could contribute to these differences (Foretz et *al.,* 2014). ALP (Alkaline Phosphatase): ALP levels were nearly identical between males (77.70 ± 11.18 U/L) and females (77.90 ± 11.80 U/L), with a p-value of 0.696, indicating no significant gender-related differences.

Table 3. Comparison of liver function tests between males and females

Items	***Experimental groups***		
(Mean± SEM)	***Male***	**Female**	P-Value
GOT (U/L)	40.0 ±74.2	20.3±8.60	0.415
GPT (U/L)	31.0 ±18.05	18.37±8.77	0.062

Discussion

This lack of statistical significance suggests that metformin therapy appears to regulate blood glucose levels similarly in both genders. However, the observed higher variability in FBS levels among males (as evidenced by a larger standard deviation) may indicate individual differences in glucose metabolism or adherence to medication and dietary recommendations. Factors such as hormonal differences and body composition could also influence FBS levels, as testosterone in males is associated with insulin resistance, while estrogen in females has protective effects on glucose metabolism [12,13]. While these findings do not show a significant gender-based difference in FBS control, the relatively small sample size (n=40 for each group) may limit the ability to detect subtle variations. Future studies with larger populations are recommended to confirm these findings and explore the underlying mechanisms contributing to potential gender differences in glucose regulation under metformin therapy [14]**.** This suggests that males may have slightly impaired renal function or higher protein metabolism compared to females, which could contribute to elevated urea levels. Other factors, such as dietary protein intake and muscle mass, might also explain these differences [15].

Females, on the other hand, generally have lower muscle mass and hence lower baseline creatinine levels [16]. The observed differences in both urea and creatinine levels highlight physiological variations between genders, which should be considered when interpreting kidney function in clinical practice. These findings suggest that males may exhibit higher baseline levels of renal function markers, even in the absence of overt kidney disease. However, the significantly higher levels in males might also reflect early signs of renal strain or reduced clearance efficiency, possibly due to higher metabolic demands or differences in metformin metabolism and excretion [17]**.** These results emphasize the importance of considering gender-specific reference ranges when evaluating kidney function. Moreover, the significant differences may provide insights into tailoring metformin dosing and monitoring strategies to optimize therapeutic outcomes for men and women with type 2 diabetes [18]**.**

This result suggests that GOT levels are relatively similar across genders in this cohort, indicating no significant gender-based differences in hepatocellular function related to metformin therapy [19]**.** ALP reflects biliary function and bone turnover; hence, these results suggest that metformin therapy does not appear to differentially affect these pathways in males and females [20]. These findings suggest that liver function, as assessed by the levels of GOT, GPT, and ALP, remains comparable between genders in type 2 diabetic patients treated with metformin. The absence of significant differences in these liver enzymes implies that metformin therapy is likely well-tolerated in both males and females with no major hepatotoxic effects [21]**.** The slight numerical differences in GOT and GPT levels may warrant further investigation with larger sample sizes to determine if these trends hold. It would also be beneficial to explore additional liver function markers to gain a more comprehensive understanding of the potential gender-specific effects of metformin therapy [22, 23].

Conclusion

The findings of this study suggest that metformin therapy is effective in managing blood sugar levels in both male and female type 2 diabetic patients. However, the observed higher levels of urea and creatinine in males highlight the need for closer renal function monitoring in male patients. No significant hepatotoxic effects were noted, indicating that metformin is generally safe for liver function in both genders. These results emphasize the value of considering gender-specific physiological and metabolic

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differences in diabetes management. Future research should include larger sample sizes and explore additional biomarkers to confirm these findings and further elucidate the underlying mechanisms of gender-related differences in metformin therapy.

Conflict of interest. Nil

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الملخص

تبحث هذه الدراسة في تأثير علاج الميتفورمين على سكر الدم الصائم(FBS) ، ووظائف الكلى (اليوريا والكرياتينين)، ووظائف الكبدGOT) ، GPT، و (ALPلدى مرضى السكري من النوع الثاني من الذكور والإناث. على الرغم من انخفاض مستويات FBS عدديًا لدى الإناث (106.8 ± 9.7 ملغ/ديسيلتر) مقارنةً بالذكور (119.7 ± 19 ملغ/ديسيلتر)، إلا أنها لم تُظهر أي فرق ذي دلالة إحصائية(p = 0.561) ، مما يشير إلى تشابه ضبط سكر الدم بين الجنسين. كشف تقييم وظائف الكلى عن ارتفاع ملحوظ في مستويات اليوريا لدى الذكور (37.40 ± 9.91 ملغ/ديسيلتر) مقارنةً بالإناث (29.37 ± 5.02 ملغ/ديسيلتر، (p = 0.041، مما قد يشير إلى اختلافات طفيفة بين الجنسين في وظائف الكلى أو استقلاب البروتين. وبالمثل، كانت مستويات الكرياتينين أعلى بشكل ملحوظ لدى الذكور (0.950 ± 0.158 ملغ/ديسيلتر) مقارنةً بالإناث (0.73 ± 0.1636 ملغ/ديسيلتر، قيمة(P = 0.007 ، مما يشير إلى ضرورة مراقبة وظائف الكلى بدقة أكبر لدى المرضى الذكور. لم تكشف معايير وظائف الكبد، بما في ذلك GOT و GPTوALP، عن أي فروق ذات دلالة إحصائية بين الجنسين. على الرغم من أن الذكور أظهروا قيمًا متوسطة أعلى لـ GOT (40.0 ± 74.2 وحدة/لتر) و GPT(31.0 ± 18.05 وحدة/لتر) مقارنةً بالإناث (20.3 ± 8.60 وحدة/لتر و18.37 ± 8.77 وحدة/لتر، على التوالي)، إلا أن هذه الفروق لم تصل إلى مستوى الدلالة) قيمة P = 0.415 وقيمة P = 0.062).كانت مستويات الفوسفاتاز القلوي (ALP) متطابقة تقريبًا بين الجنسين(p = 0.696) ، مما يشير إلى عدم وجود اختلافات مرتبطة بالجنس في أيض الصفراء أو العظام. ختامًا، يُظهر علاج الميتفورمين فعاليةً وأمانًا متقاربين في إدارة مؤشرات سكر الدم والكبد لدى كلا الجنسين. ومع ذلك، تُبرز المؤشرات الحيوية الكلوية الأعلى لدى الذكور أهمية المراقبة الخاصة بكل جنس. يُوصى بإجراء المزيد من الدراسات لاستكشاف هذه الاتجاهات على مجموعات أكبر.

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