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The Impact of Calpain-10 Gene Polymorphisms on Therapeutic Response to Metformin at the crossroad Type Two Diabetes Mellitus Patients

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ABSTRACT

Diabetes is a complex and multifaceted metabolic disorder characterized by elevated blood glucose levels resulting from either insulin resistance, insufficient insulin synthesis, or both. Metformin is often administered as one of the first oral hypoglycemic medications. The first diabetes gene to be discovered via a genome scan is the Calpain-10 (CAPN10) gene, which is linked to the onset of type 2 diabetes mellitus and insulin resistance as well as glucose metabolism and pancreatic beta-cell function. It makes the translocation of GLUT4 easier. Within the beta-cell, CAPN10 is most likely a sensor and an insulin exocytosis that acts at the plasma membrane and the mitochondria, respectively. G homozygous for the recessive model SNP-43, who had a 19% increased risk of type 2 diabetes mellitus. This prospective cohort study included one hundred patients who were recently diagnosed with type 2 diabetes mellitus. The research was conducted in Al Diwaniyah Teaching Hospital, located in Diwaniya Governorate, Iraq. The ages exhibited variation, with an average age of 55.25 and a standard deviation of 9.88. Each patient had a 12-week period between the first blood sample, which was collected at the time of diagnosis before treatment had started, and the second blood sample, which was taken 12 weeks later. Following the administration of metformin medicine, there was a significant reduction in the average BMI ($p < 0.01$). The fasting plasma glucose, plasma insulin, HbA1c, and insulin resistance (measured by the HOMA-IR index) showed a substantial drop ($p< 0.001$), whereas insulin sensitivity (measured by the QUICKI) exhibited a significant rise ($p< 0.001$). There was a significant reduction in the average lipid profile levels ($p< 0.001$), with the exception of an increase in the average HDL level. Gender disparities in glycemic control measurements suggest that males exhibit higher average values compared to women, while women demonstrate superior management of lipid profiles in comparison to men. However, it is important to note that these differences do not reach statistical significance ($p<0.05$). After three months of using metformin, we discovered a significant deterioration of glycemic control as measured by HbA1c (threshold of < 7%) ($p = 0.01$) and CAPN 10 gene SNP-43. Metformin has demonstrated efficacy in enhancing serum lipid profiles, insulin levels, fasting plasma glucose, HbA1c, the insulin resistant index (HOMA-IR), and the insulin sensitivity index (QUICKI) in individuals recently diagnosed with type 2 diabetes mellitus. A significant correlation was found between the lower response to metformin treatment and the CAPN-10 gene SNP-43.

INTRODUCTION

Diabetes mellitus includes a range of medical conditions characterized by metabolic irregularities leading to elevated amounts of glucose in the bloodstream. These anomalies may arise from a reduction in insulin production, insulin resistance, or a combination of both (Kharroubi & Darwish, 2015). Type 2 diabetes mellitus (T2DM) is a widely occurring medical condition that is often seen in individuals who are 35 years of age or older. Type 2 diabetes mellitus (T2DM) is characterized by the development of insulin resistance, accompanied with normal or excessive production of insulin during the first phases.

Over time, individuals develop beta cell malfunction and inadequate insulin production. Therefore, it may be necessary to provide insulin to some individuals in order to control their blood glucose levels throughout the advanced phases of the illness (Galicia-Garcia et al., 2020). Type 2 diabetes mellitus (T2DM) is widespread on a global scale, including in Iraq (Abusaib et al., 2020). Obesity is a significant risk factor (Leitner et al., 2017), and genetics have a significant impact in the development of the condition (Yasunaga et al., 1996). To effectively treat diabetes mellitus, it is essential to decrease body weight, apply dietary interventions, adopt lifestyle alterations, and use medication (Blaslov et al., 2018).

Metformin, a medication from to the biguanide class, is the main pharmacological treatment used to control the disease. It works by preventing the production of glucose in the liver, reducing the absorption of glucose in the intestines, and improving the body's response to insulin in certain tissues. This ultimately results in lower levels of glucose in the blood. Metformin decreases both the levels of blood glucose while fasting and after meals. Metformin is often used as a monotherapy or in combination with other treatments when dietary modifications and physical exercise are not enough to effectively cure high blood sugar levels.

As to the American Diabetes Association, metformin is the preferred medicine for recently diagnosed patients with type 2 diabetes mellitus (T2DM) who are adults or children aged 10 and older. Because of its effectiveness, safety, reasonable cost, and extensive use, it is strongly recommended as the primary therapy for type 2 diabetes mellitus (T2DM) (Davies et al., 2018). However, there is variability among people in their response to metformin as a therapeutic intervention. Studies have shown that genetic polymorphisms that are often seen may influence how metformin affects blood sugar levels.

These variations can explain up to 34% of the differences reported in the lowering of haemoglobin A1c (HbA1c) levels while taking this medicine (Zhou et al., 2014). The presence of genetic variants in pharmacokinetic genes has not consistently and substantially impacted the way people with type 2 diabetes respond to metformin, as shown in candidate gene studies (Dujic et al., 2017). Furthermore, only a restricted number of genome-wide signals associated with the clinical response to metformin have been discovered up to this point (Zhou et al., 2016).

The first diabetes gene to be discovered via a genome scan is the Calpain-10 (CAPN10) gene, which is linked to the onset of T2DM and insulin resistance as well as glucose metabolism and pancreatic beta-cell function (Alzubaidi et al., 2021). It makes the translocation of GLUT4 easier. Within the beta-cell, CAPN10 is most likely a sensor and an insulin exocytosis that acts at the plasma membrane and the mitochondria, respectively. G homozygous for the recessive model SNP-43, was had a 19% increased risk of T2DM (Song et al., 2004).

METHODS

This pretest posttest design study included one hundred patients who were recently diagnosed with T2DM (52 males and 48 females). The research started in July 2024 and concluded in January

2025. The research was conducted at the Diwaniyah teaching hospital. The diagnosis for the individuals with Type 2 Diabetes Mellitus (T2DM) was made by an endocrinologist. The age distribution exhibited variability, with an average age of 55.25 and a standard deviation of 9.88. Each patient had a 12-week gap between the first blood sample, which was collected at the time of diagnosis before treatment had started, and the second blood sample, which was taken 12 weeks later. Phenotypic analysis included collecting data on age, gender, body mass index, smoking history, family relation with T2DM, and chronic medicines for each patient. A blood sample was obtained and then split into two equal halves. One portion was allocated for the purpose of examining fasting blood sugar, serum lipid profile, and serum insulin levels, while the other portion was dedicated to genetic study and HbA1c. The HbA1c levels were measured using the Finecare™ HbA1c (Haemoglobin A1c) a Rapid Quantitative Test. The serum measurements were collected at two specific time points: the first baseline measurement and the measurement done 3 months after the initiation of metformin treatment.

Genotyping Analysis

DNA was extracted from the blood samples of all patients with type 2 diabetes mellitus (T2DM) using the Favour Prep™ Blood Genomic DNA kit (Favorgen). The DNA content and purity of the samples were evaluated using a nanodrop instrument. A polymerase chain reaction (PCR) was conducted utilising a targeted region of the genome, which was amplified using a thermocycler programme known as T-professional, produced by Biometra (Germany). The primers were supplied by Alpha-DNA as lyophilized powder. The primer sets used in this study are shown in Table 1. The 2x Taq plus PCR smart mix kit manufactured by SolGent, a company based in South Korea, was used. The setting was adjusted precisely to optimize the reaction required for DNA amplification. The PCR procedure used in this experiment began with an initial cycle at a temperature of 95 °C for a duration of 5 minutes, followed by 30 successive cycles. The process consisted of the primers being subjected to denaturation at a temperature of 95°C for a duration of 30 seconds, followed by annealing at 60°C for 30 seconds, and finally extension at 72°C for 30 seconds. The reaction was terminated by subjecting it to a final synthesis step at a temperature of 72 °C for a period of 10 minutes. The amplicon obtained from the amplification reaction was cleaved at a designated location using restriction endonucleases, using the RFLP method. The amplicon resulting from the amplification reaction was cut at a specified site using restriction endonuclease *NdeI* (Promega Corporation) and incubated at 37 °C for 1 hour by the RFLP technique. This cutting process allows for further analysis of the amplicon. The digested products were separated using 2% agarose gel electrophoresis (Condalab, Canada), which was stained with diamond nucleic acid dye that was used for coloring the gel for observation by UV apparatus.

Table 1. Sequence Primers and for Detecting the CAPN 10 Gene SNP-43

SNPs	Primers	Amplicon size (bp)
Calpain_10 rs3792267 (SNP43)	F: 5'-GCTGGCTGGTGACATCAGTGC-3' R: 5'-ACCAA GTCAG GG CTTA GCCT CACCTT CA TA-3'	G: 254 A: 223

Statistical Analysis

The data was collected, summarised, analysed, and presented using SPSS 26 and Excel 2019. A paired t-test was used to compare the means before and after treatment. The Kruskal-Wallis test was used to compare means across many groups. The gene under investigation was assessed for Hardy-Weinberg equilibrium, and a chi-square test was used to analyses the utilization of categorical data. A threshold for statistical significance was set at a value less than 0.05.

RESULTS AND DISCUSSION

The current research consisted of a group of 100 persons who were diagnosed with Type 2 Diabetes Mellitus (T2DM) and had not received any medical treatments. The patient group included 52 men (52%) and 48 females (48%). There were a total of 59 individuals who reported having a family history of diabetes mellitus. Following the administration of metformin medicine, there was a significant reduction in the average BMI ($p < 0.01$). There was a significant decrease in fasting plasma glucose, HbA1c, insulin level, and insulin resistance both before and after treatment with metformin. In addition, there was a significant improvement in insulin sensitivity as assessed by the QUICKI ($p < 0.001$). Table 2 demonstrates a significant drop in the average levels of serum triglyceride, total cholesterol, VLDL, and LDL before and after treatment with metformin. Conversely, there was a noticeable increase in serum HDL levels both before and after treatment with metformin ($p< 0.0001$).

Table 2. Comparison of Glycemic Parameters and Serum Lipid Profile Before and After Treatment with Metformin

Descriptive Statistics	Baseline Mean ± SD (n = 100)	After treatment Mean ± SD (n = 100)	P
BMI (kg/m²)	33.51 ± 8.74	30.66 ± 7.70	< 0.01
FPG (mg/dl)	245.52 ± 87.57	156.91 ± 70.02	< 0.0001
HbA1c	9.315 ± 1.60	7.00 ± 1.06	< 0.0001
Plasma insulin mIU/L	22.782 ± 7.43	15.78 ± 7.6	< 0.0001
HOMA–IR index	13.81 ± 6.94	6.17 ± 4.50	< 0.0001
QUICKI	0.271 ± 0.014	0.3 ± 0.03	< 0.0001
Triglyceride (mg/dl)	255 ± 71.2	187 ± 70.2	< 0.0001
Cholesterol (mg/dl)	219 ± 41	179 ± 30	< 0.0001
HDL (mg/dl)	37 ± 7.5	42.87 ± 7.6	< 0.0001
VLDL (mg/dl)	51.1 ± 12.94	41.3 ± 14.2	< 0.0001
LDL (mg/dl)	130 ± 41	92.16 ± 40.3	< 0.0001

The allele frequency of the CAPN 10 gene in the study was (GG = 81, G/A = 15, and AA = 4). After PCR amplification, the product of the CAPN 10 G/A was digested via the *NdeI* restriction enzyme. A 2% agarose gel was used to analyze the product, which yielded bands according to Table 1. The results are presented in Figure 1.

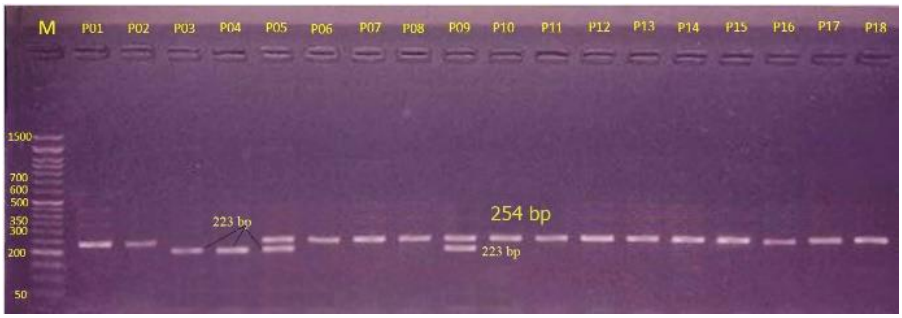

Figure 1. After Restriction Endonuclease Cleavage

polymorphic sequences were seen by electrophoresis of PCR fragments on a 2% agarose gel. The most T2DM have the wild allele SNP-43 polymorphism. In lanes 5 and 9, we can see a heterozygous carrier. In lanes 3 and 4, we can see a homozygous carrier. The observed and expected frequencies of T2DM patients for SNP-43 were significant deviations from Hardy-Weinberg equilibrium ($p = 0.0311$). To assess the impact of the SNP-43 variation on patients

glycemic response to treatment with metformin, we compared mean HbA1c levels after treatment according to the gene polymorphism, and the results show a significant difference in mean HbA1c (p = 0.01). Comparison of phenotypic characteristics, including glycemic parameters and lipid profiles, after metformin treatment according to CAPN 10 gene SNP-43 polymorphisms in the co-dominant model showed there were significant differences relevant to the variant allele, including higher values of BMI, FPG, HbA1c insulin levels, HOMA-IR, total cholesterol, and TG, in addition to a decrease of QUICKI, LDL, and HDL ($p < 0.05$) when compared with the wild and homozygous allele (see Figure 2).

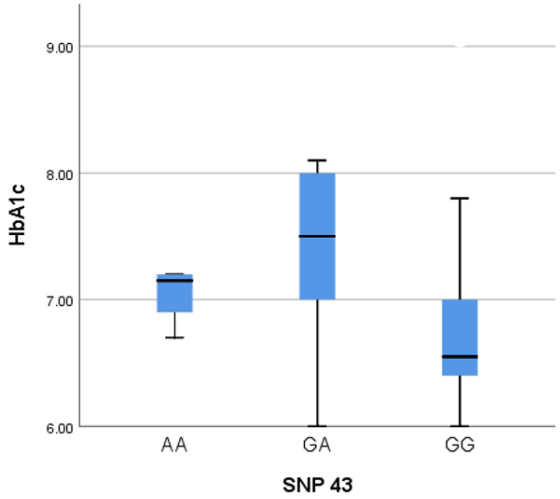

Figure 2. Independent-Samples Kruskal-Wallis Test HbA1c across SNP 43

Discussion

According to the World Health Organization's predictions, diabetes mellitus is projected to become the sixth leading cause of death worldwide by 2030 (AL-Safar et al., 2024). In general, metformin is very efficacious and distinguishes itself from other oral therapies for type 2 diabetes mellitus (T2DM) by promoting weight loss rather than weight gain. While metformin has some beneficial attributes, it is not a panacea. Empirical information derived from clinical experience and supporting research suggests that metformin monotherapy often fails to achieve glycemic control for around 21% of persons using this medicine. Therapeutic approaches fail to attain optimal levels of plasma glucose control during the first 5 years of therapy (Turner et al., 1999).

The variation in response to metformin is likely driven by genetic variables, which lead to individual differences. Following the administration of metformin in this experiment, there was a significant reduction in the average BMI ($p < 0.01$). The Diabetes Prevention Programme (DPP) is a comprehensive research endeavour that provides substantial evidence of the weight benefits associated with metformin. Out of the patients included in this study, 59.0% reported having a family history of diabetes mellitus. Individuals with a first-degree relative who has a family history of T2DM are 2 to 3 times more likely to develop T2DM compared to individuals without such a family history [19]. Those with a positive family history of diabetes mellitus have a 2.7-fold increased risk of having T2DM compared to those without a family history of diabetes (Scott et al., 2013). The present research also observed a noteworthy decrease in fasting plasma glucose, HbA1c, plasma insulin, and insulin resistance, as shown by the HOMO-IR index. The results align with previous research and are directly linked to the mechanism of metformin's effects (Thomopoulos et al., 2017).

The current study discovered that the use of metformin for a period of 3 months resulted in a substantial drop in mean blood levels of triglycerides, total cholesterol, VLDL-C, and LDL in newly diagnosed patients with type 2 diabetes mellitus. However, there was an increase in HDL-C levels. A cohort study including 155 individuals newly diagnosed with T2DM has shown the considerable efficacy of metformin in reducing triglyceride and LDL-C levels, while simultaneously increasing HDL-C levels (Lin et al., 2018). In a separate cross-sectional trial, it was shown that Metformin effectively reduced total cholesterol and LDL-C levels in 150 recently diagnosed diabetic patients who were treated for a duration of three months (Kender et al., 2019).

In the current study, following treatment with metformin analysis for BMI, glycemic parameters, and serum lipid profile values, the Kruskal-Wallis test in relation to this SNP (G/A) under the co-dominant model revealed a significant increase in BMI, FPG, HbA1c, serum insulin, HOMA-IR, cholesterol, and TG, while QUICKI, HDL, and LDL values were shown to be decreased in comparison to those of the GG and AA genotypes. These results were in agreement with a Slovakian study that demonstrated that the minor G-allele of CAPN10 rs3792269 A>G polymorphism was significantly associated with less metformin treatment success (Tkáč et al., 2015). In the same manner, patients with T2DM in Mexico were also shown to have an increased probability of therapy failure when SNP43 was considered (Garcia-Escalante et al., 2009). On the other hand, the same papers disagreed and reported that response to metformin and Sulphonylureas combination therapy enhanced in association with CAPN 10 SNP-43 led to controlled T2DM patients in South African adults (Masilela et al., 2021).

Individuals who are homozygous for the SNP-43 G variant have decreased levels of muscle CAPN10 mRNA and are more likely to experience insulin resistance. The predictive risk seems to go beyond SNP-43 and includes SNP-19 and SNP-63. These SNPs are associated with elevated blood glucose levels, slight impairment of the early insulin response, increased insulin resistance, higher BMI values, and elevated fasting TG levels in individuals with the high-risk haplotype combination (Lynn et al., 2002). A connection was observed between the heterozygosity of SNP-43 in patients with T2DM and their total cholesterol level. This correlation was shown to be stronger in heterozygous individuals compared to homozygous patients in the Gaza Strip (Zaharna et al., 2010).

CONCLUSION

The results shown that metformin had a substantial positive effect on many parameters including fasting plasma glucose, HbA1c level, serum insulin level, insulin resistance index (HOMA-IR), and insulin sensitivity index (QUICKI) in persons who were newly diagnosed with type 2 diabetes mellitus (T2DM). Similarly, metformin had a very beneficial effect on lipid profiles, resulting in a noticeable drop in all levels except for HDL, which exhibited a substantial increase. In addition, metformin significantly reduced BMI. The research revealed that after receiving metformin medication in the co-dominant model, there was a notable increase in BMI, FPG, HbA1c insulin levels, HOMA-IR, cholesterol, and TG. In addition, there was a decrease in QUICKI, LDL, and HDL. A strong connection was seen between a diminished response to metformin therapy and the presence of the CAPN-10 gene SNP-43.

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