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Review Article

Role of Genetic Polymorphisms in the Efficacy and Adverse Effects of Metformin in the Treatment of Type 2 Diabetes Mellitus

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Abstract

A clinical diagnosis of diabetes mellitus type 2 (T2DM) may include hyperglycemia, reduced insulin production, and increased insulin resistance. Conventional treatments aim to reduce the severity of disease symptoms, but they are unable to reverse disease progression or cure it. Metformin is an anti-diabetic medication for lowering hyperglycemic conditions that can be used effectively as monotherapy or in combination with other oral hypoglycemic agents. However, significant inter-individual variability is seen in the response to metformin. Although a variety of factors can affect a patient's response to medication, understanding a patient's genetic makeup could be one of the most important steps toward developing precision medicine that is more secure and effective. Pharmacogenomics-based precision medicine can improve patients' responses to anti-diabetic medications and streamline the treatment. This review aims to provide general information about T2DM, treatment challenges, and pharmacogenetic aspects of metformin. In order to meet these objectives, several studies are discussed that investigated the association between gene polymorphism and altered therapeutic response to metformin.

Keywords: Metformin, diabetes mellitus, hyperglycemia, genetic polymorphism, pharmacogenetics, precision medicine.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease marked by a continuous hyperglycemic state due to decreased insulin production and increased insulin resistance. According to the International Diabetes Federation report published in January 2015, almost 415 million people aged between 22 and 78 were living with T2DM worldwide (Zheng, Ley, and Hu 2018). According to recent estimates, over 422 million persons aged 18 and older are suffering from diabetes. The mortality rate associated with diabetes is 1.5 million per year, and there are chances of a significant increase in this rate in the coming years globally. By 2030, diabetes is anticipated to rank as the seventh-leading cause of mortality, with over 600 million people predicted to have this condition (Rowley et al. 2017). Under-developed countries, particularly those in sub-Saharan Africa (Wild et al. 2004), are predicted to experience a more than two-third increase in the incidence of diabetes.(Azevedo and Alla 2008) From an estimated 7.1 million people in the early 2000s to a projected 18.6 million by 2030, the disease's impact in Africa has expanded dramatically (Dodu 1958).

Diabetes is a major burden on global public health (Malek et al. 2019). Diabetic patients may experience damage to various organ systems due to chronic hyperglycemia, which, in conjunction with other metabolic abnormalities,

generates life-threatening consequences. These consequences include micro-vascular nephropathy and retinopathy, along with major macro-vascular complications, increasing the

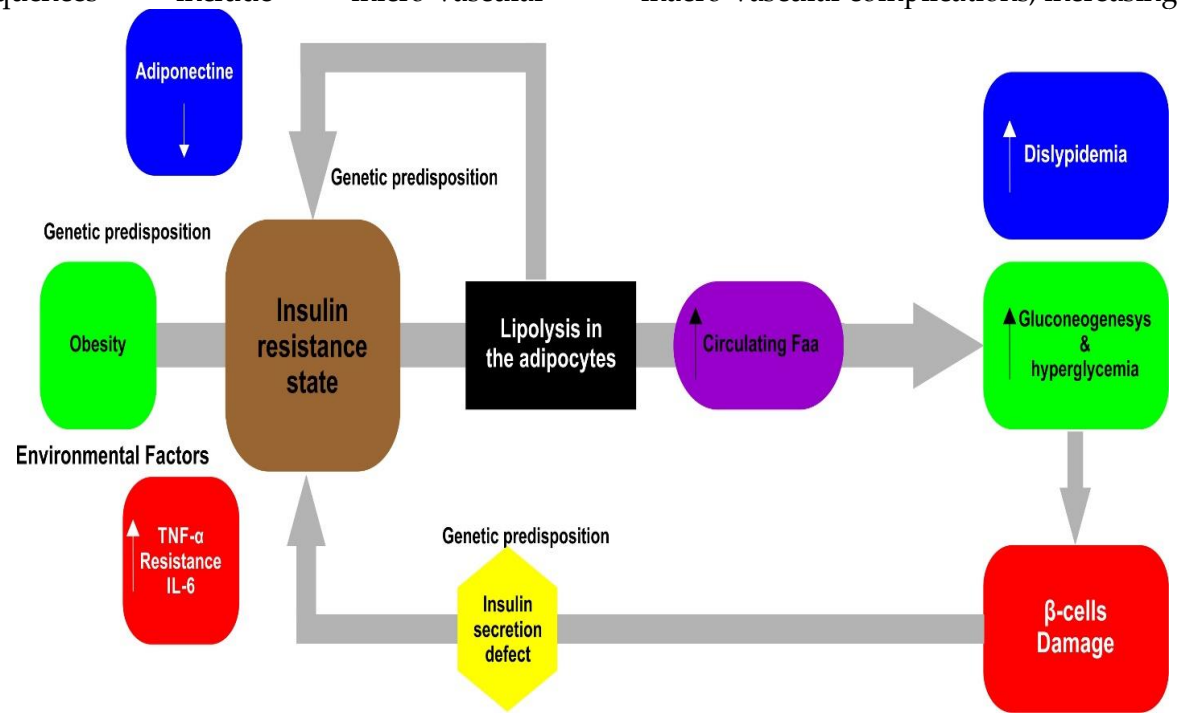

Figure 1: Pathophysiology of T2DM (As per Artasensi et al; 2020)

risk of cardiovascular diseases. However, effectively controlling the underlying symptoms through appropriate medications may reduce the risk of complications and mortality linked to this disorder. Metformin is a widely accepted first line of treatment by most clinicians due to its better tolerance and safety profile. Therapeutic responses to this agent vary among individuals, possibly due to gene polymorphism, among other factors. This review aims to provide general information about T2DM and a compilation of various studies conducted during the last ten years to investigate the impact of gene polymorphism on metformin treatment outcomes.

2. Prevalence and Risk Factors

Diabetes is a complex illness having significant heterogeneity(Lipscombe and Hux 2007, Organization 1999). This condition has affected almost 5 to 10 percent of people globally (Alqurashi, Aljabri, and Bokhari 2011) (Al-Nozha et al. 2004). Therefore, it is one of the most prevalent chronic endocrine ailments. Numerous studies have predicted a rise in diabetes mellitus, especially in emerging nations. Between 2010 and 2030, the number of people with diabetes is anticipated to increase by 20% and 69% in industrialized and developing countries, respectively (Shaw, Sicree, and Zimmet 2010). By 2030, there may be 439 million people with diabetes, and 7.7% of those will be aged between 20 to 79 (Atlas 2015). Numerous studies demonstrate that lifestyle changes can successfully stave off diabetes and obesity in high-risk persons having hyperglycemia (Zimmet, Alberti, and Shaw 2001).

The east Mediterranean area has the second-highest prevalence of diabetes worldwide. Nearly 25% of the people in this region have diabetes, according to the World Health Organization (WHO) (Thelin and Holmberg 2014). A high prevalence of T2DM was found in the Gulf. In Bahrain, Oman, and Kuwait, the

prevalence rates were found to be 25.7%, 16.1%, and 21%, respectively (Zimmet, Alberti, and Shaw 2001). A public health crisis is brewing in Saudi Arabia, where the number of diabetic patients has gradually risen for several decades (SS 2016). The indirect financial burden of diabetes mellitus on the country is expected to be in excess of 870 million USD, and persons with diabetes experience healthcare expenses that are over ten times greater ($3686 vs. $380) than those without the disease (Atlas 2015). It has been demonstrated that Asians experience greater incidence rates than white Americans or white Britons, with black people experiencing the highest risk (Health 1995).

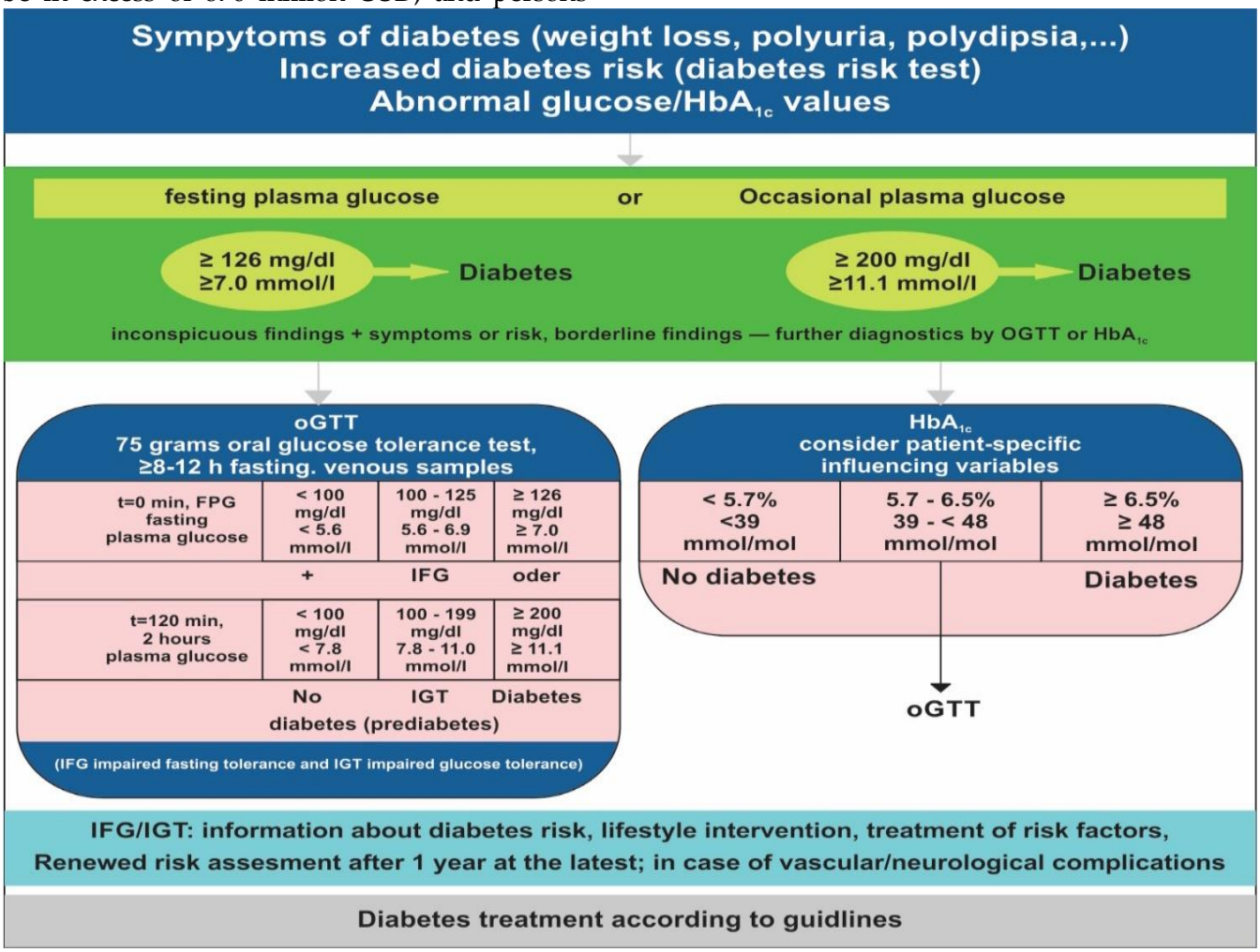

Figure 2: Flow sheet diagnosis of diabetes.

Several genetic studies of T2DM during the past ten years have shown the complex polygenetic nature of the disease (Fuchsberger et al. 2016, Zheng, Ley, and Hu 2018). The majority of these loci enhance T2DM risk by having primary effects on insulin production. Despite lacking a definite cause, several other relevant variables have been identified, including contemporary lifestyle factors (which encourage obesity), socioeconomic factors, direct genetic predispositions, and gene-environment interactions. Genetic susceptibility has a considerable impact on the likelihood of getting T2DM.

Studies have shown that several lifestyles might be important in causing diabetes (Musaiger, Al-Awadi, and Al-Mannai 2000). The big risk factors for T2DM are little exercise and high

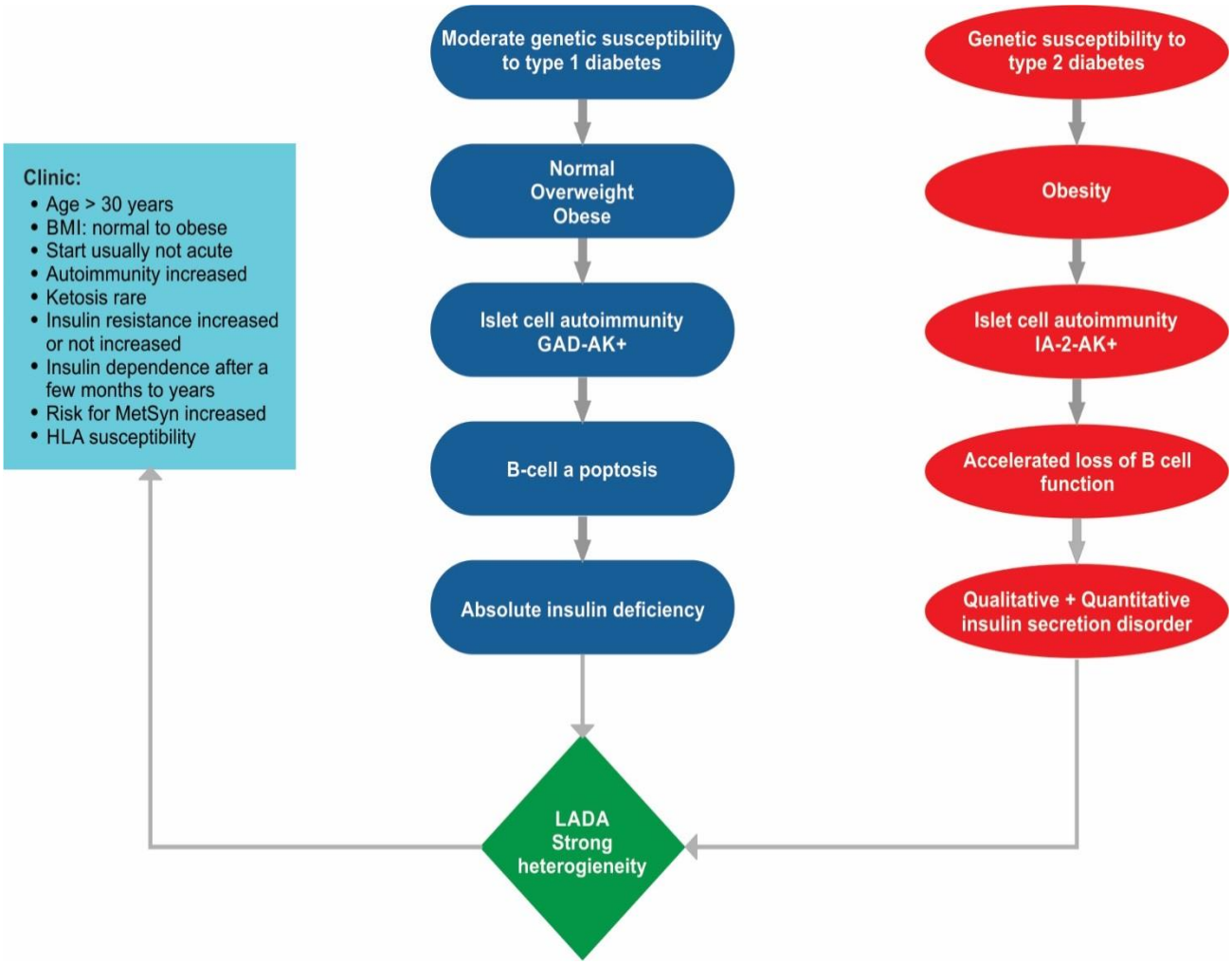

Figure 3: Criteria for LADA diagnostic

body mass index (BMI) 30 kg/m2), which is also linked to metabolic abnormalities that lead to pathological complications (Lee et al. 2011). The age of T2DM diagnosis and BMI had an inverse linear association (Ansari 2009). However, several variables have demonstrated a key involvement in this pathological process's progression, including both cell-autonomous processes and inter-organ interactions (Manson et al. 1992).

3. Pathophysiology of Diabetes

In diabetes, unusually higher blood glucose levels are due to an imbalance between insulin action and secretion (Stumvoll, Goldstein, and Van Haeften 2005). Due to beta-cell (B-cell) dysfunction, the body's ability to maintain normal glucose levels is compromised, resulting in decreased insulin secretion. On the other side, increased hepatic glucose production and decreased glucose uptake in adipose tissue, muscle, and the liver occur during early-stage pathophysiology, which assists the progression of the disease. However, B-cell disruption is more critical in diabetes (figure 1). Hyperglycemia due to B-cell dysfunction leads to the development of T2DM (Cerf 2013). Hyperglycemia is closely related to physiological and behavioral reactions. Whenever one is hyperglycemic, the brain detects it and sends a signal to the pancreas and other organs to lessen its impact (Weinstein et al. 2004).

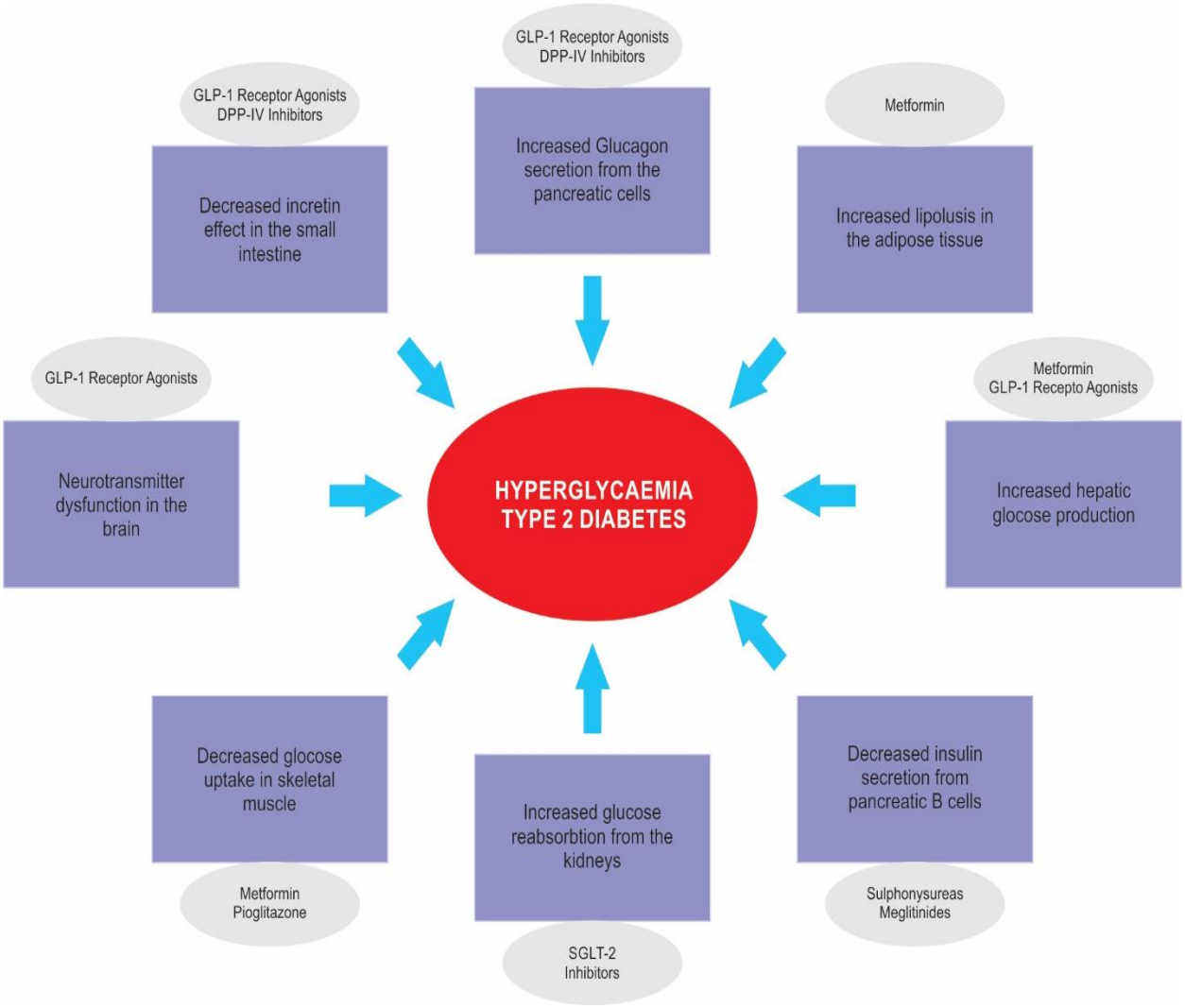

Figure 4: Target sites for hyperglycemic treatments.

Type-1 diabetes mellitus (T1DM) is manifested through the invasion of CD 4/8 + lymphocytes and macrophages affecting pancreatic cells resulting in low insulin production. There are a number of characteristics that make it an autoimmune disease (Venkatasamy et al. 2013).

- Involvement of immune-competent cells in islets cells of the pancreas.
- Linkage of disease between Class II genes and major histocompatibility complex.
- Presence of islet cell-specific autoantibodies

Before starting insulin therapy, the majority of patients had detectable anti-insulin antibodies, and around 85% of patients had circulating islet cell antibodies. The glutamic acid decarboxylase, found in pancreatic B-cells, is the major target of islet cell antibodies (Strasser 2013).

The metabolic abnormalities associated with T1DM are caused by a lack of insulin production caused by the autoimmune death of pancreatic β-cells. In addition to reducing insulin secretion, T1DM patients also have aberrant pancreatic alpha-cell activity and increased glucagon release. In healthy people, hyperglycemia reduces glucagon secretion; however, in people with T1DM, hyperglycemia does not affect glucagon secretion (Ross 2003). The metabolic abnormalities brought on by an inadequate

Figure 5: T2DM (Based on National Institute of Health (NIH) and ADA recommendations)

supply of insulin are made worse by the abnormally increased glucagon levels.

Due to a deficiency in insulin production, lipolysis remains unchecked, leading to higher plasma fatty acid levels. This inhibits glucose metabolism in peripheral tissues, such as skeletal muscles (Ross 2003). Consequently, glucose uptake is reduced, and insulin deprivation also results in decreased expression of several genes, including those for glucokinase, which is present in liver cells, and the main class of glucose transporters, known as GLUT4, found in adipose tissue. These genes are essential for target tissues to respond to insulin when needed (Ross 2003).

4. Management of Diabetes

For T2DM, metformin is the most comonly prescribed oral anti-hyperglycemic agent, as it shows promising results in lowering blood glucose levels. Its mechanism of action involves a decrease in hepatic glucose synthesis. Several recommendations, including those of the American diabetes association (ADA) (figure 5) and the European Association for the Study of Diabetes, now suggest it as first-line therapy. Its attributed position is due to its efficiency, cost, weight neutrality, and positive safety profile. Improvements in certain lipid profiles, lowering inflammatory markers, and decreasing cardiovascular events have all been mentioned as additional advantages besides the medication's ability to lower blood sugar. (Sanchez-Rangel and Inzucchi 2017). Glucose-lowering target therapies are shown (Figure 4).

5. Gene Polymorphism & Metformin

Various diseases, including cardiovascular diseases, neuropathy, renal failure, and blindness, may follow T2DM; therefore, the importance of effectively controlling hyperglycemia in diabetes patients is

necessary(Ghasan Abood Al-Ashoor et al. 2022). According to a meta-analysis (Mofo Mato et al. 2018) metformin is the first drug of choice in T2DM. However, the response is not the same among all individuals. It is reported that almost 35% of patients fail to achieve desired hyperglycemic control. One of the factors behind these fluctuating responses to metformin may involve gene polymorphism of those genes involved in regulating the pharmacodynamics and pharmacokinetics of metformin, which may alter its efficacy and related side effects (Ningrum, Istikharah, and Firmansyah 2019). Moreover, the variability in response among the various ethnicities may depend on the frequency of associated pharmacogenomic risk alleles (Mofo Mato et al. 2018). This review encompasses the studies that investigated associations between alterations in genes encoding transporters involved in metformin pharmacokinetics as well as dynamics such as organic cation transporter 1 *(OCT1), OCT 2, OCT 3*, multidrug and toxin extrusion1 (*MATE1),* ataxia telangiectasia mutated (*ATM).*

Table 1. Important studies showing the influence of genetic variation on the therapeutic efficacy and adverse effects of metformin in T2DM.

Gene	Polymorph showing a positive association with metformin	References
OCT 1/ SLC22A1	Met420del	(Mahrooz et al. 2015)
	rs622342	(Umamaheswaran et al. 2015)
	rs1867351 T/T or rs4709400 G/G genotype	(Zhou et al. 2015)
	A allele of the rs628031 and 8 bp insertion rs36056065	(Tarasova et al. 2012)
	(rs12208357) and M420del (rs72552763)	(Dujic et al. 2016)
	G/G and A/G genotypes of rs628031 and rs461473	(Altall et al. 2019)
	rs622342	(Wu et al. 2020)
	156T>C and 1222A>G (responders), 181C>T and 1201G>A (non-responders)	(Kawoosa et al. 2022)
	rs622342, rs628031, rs594709	(Chen et al. 2022)
	rs1208357	(Nasykhova et al. 2022)
OCT2/ (SLC22A2)	rs316019	(Yoon et al. 2013)
	rs316019	(Islam et al. 2018)
	rs5393, rs5400	(LIU, YANG, and YIN 2020)
OCT3/ SLC22A3	rs12194182	(Al-Eitan et al. 2019)
MATE1/SLC47A1	rs36056065	(Zhou et al. 2015)
	rs2252281	(Mostafa-Hedeab et al. 2018)
ATM	rs11212617	(Altall et al. 2019)
	rs11212617	(Chen et al. 2022)

5.1. OCT 1/ (SLC22A1)

Many studies highlight the polymorphic nature of *OCT1*. Uptake of metformin by hepatocytes mainly occurs via *OCT 1* (Chen et al. 2022); therefore, polymorphism in genes encoding this transporter may alter the therapeutic response. In a study, 08 newly diagnosed diabetic patients on metformin monotherapy were recruited to find an association between *OCT1* Met420del polymorphism and hyperglycemic control after therapy. Subjects were divided into responders ($n = 49$) and non-responders ($n = 59$) based on their response to metformin, assessed by measuring Hb1AC levels. The restriction fragment length polymorphism technique detected *OCT1*-Met420del polymorphism in genomic DNA. A significant contribution of *OCT1*-Met420del variant was observed in changing response to metformin therapy (Mahrooz et al. 2015).

Another study was designed to evaluate the association of *SLC22A1* rs622342 gene polymorphism with the clinical efficacy of metformin in South Indian T2DM patients. 122 patients, newly diagnosed with T2DM, irrespective of their gender, were selected for the study. Metformin monotherapy was initially started for patients' hyperglycemic control for 12 weeks. Real-time polymerase chain reaction (qRT-PCR) was used for genotyping. Based on HbA_{1c} levels, patients were marked as responders and non-responders. The frequency of variant allele 'C' (AC) of rs622342 polymorphism was more pronounced in non-responders when compared to the responders. This lack of response was more conspicuous among carriers of 2 copies of 'C' alleles. On the other hand, carriers of two copies of 'A' allele showed better response to the treatment. This data suggests that *SLC22A1* rs622342 gene polymorphism is significantly linked to metformin treatment response in South Indian patients diagnosed with T2DM (Umamaheswaran et al. 2015).

(Zhou et al. 2015) evaluated the effects of the *OCT1* single nucleotide polymorphisms (SNPs), rs1867351, rs4709400, rs628031, and rs2297374, on metformin efficacy in T2DM patients. They performed a single-center prospective analysis of the distributions of these SNPs in a cohort of Han Chinese subjects in Shanghai, China. The association of SNPs with patients' responses for three months of metformin treatment was analyzed. Patients having rs1867351 T/T or rs4709400 G/G genotype showed greater response to treatment as assessed by measuring reductions in postprandial plasma glucose (PPG). Substantial reduction in fasting plasma glucose was observed in patients having genotype rs2297374 C/T, rs4709400 G/G, or rs628031 G/G, while those with the rs1867351 T/T, rs628031 A/A, or rs2297374 C/T genotype showed significant reductions in HbA_{1c}.

Most studies highlighted gene polymorphism's influence on metformin's pharmacokinetic and pharmacodynamics parameters, while little is explored about their implication in side effects related to metformin. Almost 20-30% of patients experience gastrointestinal side effects, and 5% are unable to use metformin due to the severity of adverse effects (Tarasova et al. 2012) investigated how gene alteration increases or decreases the incidence of metformin-associated side effects. A significant association was observed between the A allele of the rs628031 and also 8bp insertion (rs36056065) in the *OCT1* gene.

A study explored the association between OCT1-reduced activity polymorphism and metformin-associated adverse effects in T2DM patients on metformin treatment (Dujic et al. 2016). Genotyping was done for loss of function variants in the *OCT1* gene (*SLC22A1*): R61C (rs12208357) and M420del (rs72552763). A positive association was observed between *OCT1* gene-reduced function variants and the side effects of metformin. The exact mechanism involved in metformin-induced side effects is unclear. However, the high local concentration

of metformin in the intestine due to the reduced function of *OCT1* may be the reason (Dujic et al. 2016).

According to the ranking in the Middle East/North Africa region, Saudi Arabia is fourth in diabetes prevalence. A study was conducted in western Saudi Arabia to investigate any association between gene polymorphs of *SLC22A1* (rs628031 and rs461473) and response to metformin treatment (Altall et al. 2019). They deduced that G/G and A/G genotypes of rs628031 and rs461473 variants of *SLC22A1* are significantly associated with uncontrolled hyperglycemia after metformin use. Therefore, G was predicted to be the risk allele among the assessed *SLC22A1* variants. (Wu et al. 2020) also detected that the *SLC22A1* rs622342 gene variant could be related to insulin sensitivity when patients are treated with metformin in a study conducted on genetically unrelated Chinese patients recruited from the Endocrinology Department, Shandong Provincial Qianfoshan Hospital from April 2018 to May 2019. Subjects were receiving metformin for at least six months. Another study aimed to find an association between variable therapeutic response to metformin and *OCT 1* polymorphism recruited 41 patients diagnosed with T2DM. The participants of the study were divided into responders and non-responders. Two SNPs (156T>C and 1222A>G) detected through genotyping were common in responders and non-responders, while 181C>T and 1201G>A were present exclusively in non-responders. The possibility of *OCT1* polymorphism influence on metformin efficacy was further corroborated by the results of this study (Kawoosa et al. 2022).

(Reséndiz-Abarca et al. 2019) designed a study to find a link between genetic variants in the *SLC22A1* gene (rs622342, rs628031, rs594709) in T2DM patients showing altered therapeutic response to metformin. 308 T2DM patients on metformin monotherapy were recruited for a cohort study. HbA_{1c} levels were measured at the start of the study, then after six months and 12 months. A significant association was detected among genotypes CC-rs622342, AA-rs628031, and GG-rs594709 in the *SLC22A1* with increased HbA_{1c} levels during the follow-up period. This indicates the genetic variation in the *SLC22A1* gene was significantly related to the variation of the HbA_{1c} levels, an important indicator of glycemic control in diabetic patients. These results were further corroborated by (Chen et al. 2022), who found a positive association between the most frequent variant of *SLC22A1* rs622342 and response to metformin treatment in T2DM of Han nationality in Chaoshan, China.

The influence of *SLC22A1* gene variant rs1208357 on response to metformin treatment was investigated through a cohort study that recruited 464 unrelated T2DM patients and 129 healthy subjects (Nasykhova et al. 2022). The results showed a significant impact of rs1208357 in the *SLC22A1* gene on response to metformin in T2DM patients.

5.2. OCT2/ (SLC22A2)

Secretion of Metformin in kidneys is facilitated by *OCT 2* present on the basolateral membrane of proximal epithelial cells. Therefore, metformin's pharmacokinetic and pharmacodynamic effects could be influenced by the polymorphism of genes encoding *OCT2* (Borra et al. 2023). (Yoon et al. 2013) investigated the impact of polymorphisms in genes encoding *OCT-2* on metformin pharmacokinetics. *OCT2*-808 G>T (rs316019) significantly altered the pharmacokinetics yielding a higher peak concentration with a larger area under the 'serum time concentration curve.'

rs316019 (c.808G>T, p.270A>S) is one of the most frequently occurring variants of genes *SLC22A2* and significantly influences metformin pharmacokinetics. According to (Islam et al. 2018), dose adjustment in *SLC22A2* variants could be useful for improving the efficacy of metformin and reducing its side effects. Another study investigated the association of *SLC2A2* rs5393, rs5400 loci gene polymorphism with the therapeutic response to metformin in T2DM

patients(LIU, YANG, and YIN 2020). The results showed that T2DM patients with AA type at rs5393 locus and CC type at rs5400 locus of *SLC2A2* gene polymorphism loci are sensitive to metformin and have good hypoglycemic effects.

5.3. OCT3/ SLC22A3

(Al-Eitan et al. 2019) studied the relationship between the SNP of the *SLCA3* gene encoding OCT3 and the response of metformin monotherapy in Jordanian T2DM patients. The results indicated a significant ($p<0.05$) impact of rs12194182 SNP in the *SLC22A3* gene on effective control of hyperglycemia by metformin, confirmed through HbA_{1c} levels. Patients having the CC genotype exhibited a more pronounced association (Al-Eitan et al. 2019). According to (Ghasan Abood Al-Ashoor et al. 2022), *OCT3* (rs2292334) could be considered a possible genetic risk factor for the development of T2DM among Indian males alone.

5.4. Multidrug and Toxin Extrusion1 *MATE1*/SLC47A1

MATE-1 protein, predominantly located in the apical membrane of renal tubule and canalicular cells of hepatocytes, is encoded by the *SLC47A1* gene. These proteins are responsible for transporting metformin to bile through hepatocytes and excreting it via kidneys (Ningrum et al. 2022).

The association of a polymorphism in *the SLC47A1* gene (rs36056065) encoding MATE-1 proteins was observed in 153 patients diagnosed with T2DM in China. Polymerase Chain Reaction (PCR), with primers, was designed to amplify the DNA fragment that had selected polymorphism. However, the study's results were inconclusive (Zhou et al. 2015). On the other hand, Egyptian patients newly diagnosed with T2DM were observed to find the association of SNP (rs2252281) with metformin effectiveness. The patients did not receive any medication before selection for the study. It was concluded that carriers of CC and TT alleles had better control of the hyperglycemic state when compared to carriers of CT alleles. The results indicated an impact of *MATE-1* SNP in therapeutic response to metformin (Mostafa-Hedeab et al. 2018).

5.5. Ataxia telangiectasia mutated (*ATM)* gene

Glycemic control in T2DM is found to be significantly altered in the presence of *ATM* gene polymorphism (rs11212617). The *ATM* gene regulates the DNA repair, cell cycle, and activation of protein kinase that controls hyperglycemia in diabetic patients (Zhou et al. 2011). The influence of polymorphism in *the ATM* gene on treatment response to metformin was investigated in Saudi T2DM patients. A significant correlation was observed between A/A and A/C genotypes of the rs11212617 polymorphism of *ATM* and elevated HbA_{1c}. The result showed the possibility of *ATM* gene polymorph involvement in controlling hyperglycemia in T2DM patients through metformin (Altall et al. 2019). Similarly, in another study, 82 Chinese patients diagnosed with T2DM on metformin monotherapy showed a positive association of *ATM* (rs11212617) with metformin therapeutic response was observed (Chen et al. 2022).

6. Conclusions & Recommendations

Hyperglycemia is the hallmark of T2DM, one of the most prevalent health problems in the world, which can lead to life-threatening consequences, including blindness, cardiovascular diseases, stroke, renal failure, and neuropathy, if left untreated. Moreover, damage to cerebral vessels may cause brain atrophy and ultimately lead to vascular dementia. Metformin is considered the first drug of choice, either as monotherapy or combined with other glucose-lowering agents, in T2DM. Metformin is a well-tolerated, safe, and effective choice in most cases. However, not all patients achieve the same level of hyperglycemic control. The literature review shows that 35% of patients exhibit deviation from a normal response to treatment with

metformin. Genetic factors may explain the heterogeneity in response to metformin therapy. Pharmacogenomic studies on metformin may aid clinicians in personalizing anti-diabetic medications and selecting appropriate drugs based on patients' genetic profiles. In this review, we compiled several studies conducted to detect an association between the polymorphism of genes and their influence on pharmacokinetic and pharmacodynamic parameters. However, other genes contributing to these anomalies may remain unexplored. Additionally, confirming these findings through clinical translation is still lacking and requires further consideration.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Authors Contribution

MBR conceptualized the study and wrote the final manuscript, YCC helped in the analysis and writing the first draft, did the literature review, and MBR supervised the whole project.

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