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DIABETES MELLITUS IN WOLFRAM SYNDROME 1: CHARACTERISTICS AND PERSPECTIVES IN TREATMENT

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ABSTRACT

Wolfram syndrome 1 is a rare autosomal recessive disorder caused by mutations in the WFS1 gene related to endoplasmic reticulum (ER) function. The course of the disease most often begins with diagnosis of insulin-dependent non-autoimmune diabetes mellitus with an early onset. Its clinical character is presented with an acronym DIDMOAD: diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and deafness (D).

This article focuses on the clinical features of diabetes mellitus in Wolfram syndrome. We also describe current approach to its therapy and discuss possible treatment options placing the main emphasis on the GLP1 receptor agonists and cell regenerative therapy.

Methods and materials: A qualitative synthesis of the data focusing on GLP-1 agonists, cell regenerative therapy and diabetes mellitus in Wolfram syndrome was performed. This literature review of GLP-1 receptor agonists and cell regenerative therapy effect on metabolic control, and current perspectives of treatment in patients with Wolfram syndrome, a monogenic type of diabetes, included recent publications, primarily from the past 10 years, and was conducted from November 2025 to April 2026 using the PubMed database.

A systematic search was performed using specific keywords and medical subject headings (MeSH terms) related to GLP-1 agonists and Wolfram syndrome. The primary search terms included: “diabetes mellitus”, “GLP-1 agonists”, “Wolfram syndrome”, “WFS1”, “monogenic diabetes”, “islet transplantation”, and “cell regenerative therapy”. The criteria for inclusion of articles were as follows: published before April 2026, written in English, peer-reviewed original research articles. Exclusion criteria included publications not available in full text, articles in languages other than English. Editorials, commentaries, and conference abstracts without full data were also excluded. Titles and abstracts of the retrieved articles were screened to determine eligibility based on the inclusion and exclusion criteria.

KEYWORDS

Cell Regenerative Therapy, GLP-1 Receptor Agonists, Wolfram Syndrome 1, Diabetes Mellitus, Islet Transplantation

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Abbreviations:

GLP-1, glucagon-like peptide-1; WS, Wolfram syndrome; WS1, Wolfram syndrome 1; DMWS, diabetes mellitus in Wolfram syndrome; DM1, diabetes mellitus type 1; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; CSII, continuous subcutaneous insulin infusion.

Introduction:

Wolfram syndrome (WS; MIM 222300) is a neurodegenerative disease with autosomal recessive inheritance which can be classified into 2 types: Wolfram syndrome 1 (WS1; MIM 606201) and Wolfram syndrome 2 (WS2; MIM 604928). Due to its prevalence being described as 1 in 500.000, WS is often categorized as rare/very rare disease (Du et al., 2023; Rigoli et al., 2022). It affects approximately 15.000 to 30.000 patients worldwide (Resta et al., 2023). Although the type of inheritance is primarily autosomal recessive, it is worth noting that there have been described mutations in autosomal dominant mode which are responsible for WS (Pallotta et al., 2019). Mutations in genes *WFS1* and *WFS2* are the main cause of the disease (Serbis et al., 2023). The *WFS1* gene is located on chromosome 4p16 and encodes wolframin, a transmembrane protein localized to the ER (endoplasmic reticulum). Mutations in the *WFS1* gene are a genetic cause of WS1. They are leading to ER stress and later beta cell dysfunction (Feingold, 2025). The consequence of neurological and respiratory dysfunction progression is death at median age of 39 (Iafusco et al., 2022; Jurca et al., 2024; Rigoli et al., 2018). Wolfram syndrome 2 on the other hand is caused by mutations in *CISD2* gene located on chromosome 4q22 (Rigoli et al., 2022; Rigoli & Di Bella, 2012). *CISD2* protein (iron-sulfur domain-containing protein 2) is mostly expressed in mitochondria-associated ER membranes (Delprat et al.,

2018). The clinical picture of WS1 syndrome is accurately characterized by acronym DIDMOAD – diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and deafness (D). Clinical guidelines for the management of WS as well as criteria for WS and WS-like disorders were proposed by EURO-WABB (Li et al., 2023). To make a diagnosis of WS, necessary condition must be fulfilled – simultaneous occurrence of DM (early onset of insulin-dependent non-autoimmune diabetes mellitus) and OA (bilateral optic atrophy), which are also classified by many authors as major criteria of this syndrome, with DM being present in 98.21%, and OA in 82.14% cases of WS respectively (Rigoli et al., 2022; Rigoli & Di Bella, 2012). Among the other symptoms associated with DIDMOAD in patients with WS the most common are sensorineural hearing loss (48.2%) and diabetes insipidus (37.7%). Apart from the DIDMOAD symptoms, the clinical manifestations may also include urinary tract complications (19.39%) – neurogenic bladder, bladder incontinence, urinary tract infections (UTIs); neurological symptoms (17.09%) – central apnea, ataxia, dysphagia, areflexia, epilepsy, decreased ability to taste and detect odors, headaches, orthostatic hypotension, hyperpyrexia, hypothermia, constipation, gastroparesis. Other common clinical features contain psychiatric symptoms (44.4%) – anxiety, panic attacks, depression, mood swings, sleep abnormalities, psychosis; and endocrinological disorders (6.6%) – hypogonadism, deficient growth hormone secretion, corticotropin deficiency, delayed menarche in female (Rigoli et al., 2022).

Aim of the study:

In this literature review, the aim is to provide an integrated overview of diabetes mellitus in Wolfram syndrome and assess current perspectives of GLP-1 receptor agonists and regenerative therapy in treatment of diabetes mellitus in Wolfram syndrome.

1. Diabetes mellitus in Wolfram syndrome (DMWS).

Diabetes mellitus in Wolfram syndrome differs widely from typical clinical character of type 1 diabetes mellitus (DM1) among juvenile patients. It is often described as insulin-dependent non-autoimmune diabetes mellitus with an early onset with diagnose by mean at the age of 6 (range: 3 weeks – 16 years old). In contrast to the autoimmune process directed against the beta cells of the pancreas in DM1, diabetes in Wolfram syndrome results from a primary defect in these cells (Catarinella et al., 2025). It has been shown that the highest risk of developing DM was among children in their first 2 decades (34% at the age of 10 and 38% at the age of 16). In 64% cases of WS, DMWS began in the first decade, also typically being the first clinical manifestation of WS (Bueno et al., 2018; de Muijnck et al., 2023; Rigoli et al., 2022). The major difference between DMWS and DM1 is much rarer ketoacidosis at the onset of diabetes, as well as earlier diagnosis, longer remission periods, lower daily requirements of insulin, better metabolic control (lower mean values of HBA1c) and more frequent episodes of hypoglycemia (Iafusco et al., 2022). Below we describe the most characteristic clinical features that distinguish DMWS from DM1.

1.1. Rarer ketoacidosis.

Although diabetic ketoacidosis (DKA) is potentially life-threatening complication of DM1 with mortality rates less than 1%, it can also be present in DMWS (Evans, 2019). Despite this, many studies confirm that DKA in DMWS shows lower prevalence and is often absent at the onset of diabetes (Iafusco et al., 2022), (Duan et al., 2018). In one study which consisted of 5 patients with WS and DMWS there was no instance of DKA. Study by Lian Duan et al. which included 6 patients with DMWS also found no evidence of ketosis (Duan et al., 2018). However, in one multicenter study, the incidence of DKA with pH < 7.3 in DM1 patients were 20% (n=13,644), followed by 7% (n=41) in DMWS with p value of 0.049 (Rohayem et al., 2011). These results clearly indicate that if a sufficiently large group of patients is assessed, the rate of DKA is more common, but still significantly lower compared to DM1.

1.2. Longer remission periods.

The main pathomechanism leading to the development of DM1 is an autoimmune process directed against the beta cells of the pancreas causing their irreversible destruction. However, the remission phase in DM1 occurs in few patients during the progression of diabetes. Some patients may experience a “honeymoon phase”, often described as phase of partial remission (PR) which refers to transient phase of improved glucose control during which islet beta cells continue production and secretion of insulin. This results in lowering the exogenous insulin requirements measured by IU/kg/day and improves glycemic control. The PR phase shows a potential therapeutic opportunity to slow down the progression even cure the diabetes before the development of its chronic

complications. A similar phenomenon can be observed in DMWS (Zhong et al., 2020), (Gomez-Muñoz et al., 2024), (Collier et al., 2025). In a study by Julia Rohayem et al. the authors observed that the average duration of diabetes remission (years) in DMWS patients was 2.3 ± 2.4 compared to 1.6 ± 2.1 in DM1 ($p = 0.064$) (Rohayem et al., 2011). Although it did not reach statistical significance of p value < 0.05, their study show that time of remission period may vary. Additionally, some studies indicate that there are described cases of DMWS with extremely long remission periods of 8 years (Iafusco et al., 2022), (Fishman & Ehrlich, 1986).

1.3. Better metabolic control and lower daily requirements of insulin.

Glycated hemoglobin (HBA1c) is the most important factor that is generally used by physicians to assess and evaluate glycemic control, including long-term, in patients with all kinds of diabetes. HBA1c has become a standard in monitoring individuals with diabetes and correlates with the development of complications, however it should not be interpreted with isolation but with comprehensive assessment of patient. HBA1c ≥ 6.5 % (48 mmol/mol) is a validated method of diagnosing a diabetes because it reflects the average blood glucose concentration over the last 3 month, with the glucose concentration from the last month having the greatest influence (M. Wang & Hng, 2021). Results of study by A. Zmyslowska et al. showed that the average HbA1c level among 11 enrolled participants was 7.55 (7.2–8.3) (Zmyslowska et al., 2020). However, descriptive, cross-sectional observational study by Mary K.R. et al. which took place from 2010-2019, consisted of 44 patients (25 female, 19 male) with clinically confirmed WS, has shown that mean HBA1c from all measurements of participants was 7.9% (Ray et al., 2022). Overall, studies revealed that the value of HBA1c in DMWS may range from 6 to 9.3% with an average value of 7.5% (Iafusco et al., 2022).

A significant difference between DM1 and DMWS is the tendential to better glycemic control in the latter. The improvement in metabolic control is primarily due to a lower daily requirement of insulin. In a study by Toppings et al. total daily requirements of insulin were 0.71 ± 0.07 IU/kg/day in DM1 versus 0.88 ± 0.04 IU/kg/day in DMWS patients with a p-value of 0.0325. Authors suggest that lower daily dose of insulin in patients with WS might be due to greater pancreatic beta-cell reserve and better insulin sensitivity in comparison to DM1 patients (Toppings et al., 2018).

1.4. More frequent episodes of hypoglycemia.

Hypoglycemia is a common complication of diabetes, classified as lower than physiological blood glucose concentration of ≤ 70 mg/dl (or ≤ 3,9 mmol/l). Frequency of hypoglycemia among patients may vary depending on their technique of insulin injection, overall metabolic control (described before) and food taken. Some studies estimated that among patients with DM1, the episodes of hypoglycemia occur between 42 to 91 events per patient-year (Cockcroft et al., 2020). DMWS and nervous system disorders, both of which often coexist in WS, may lead to the ER dysregulation and diabetic autonomic neuropathy, similar to DM1, and cause hypoglycemia. In a multicenter study by Julia Rohayem et al., researchers reviewed clinical data of 50 patients with DMWS and compared them with the data of over 24 thousand patients with DM1. They found out that the neurology system disorder in the WS group with a mean HBA1c > 7.5% ($p = 0.031$) in the comparison to DM1, progressed much faster. They have also discovered that occurrence of severe hypoglycemia among DMWS patients were almost 5 times greater than DM1 patients (DMWS – 37%, DM1 – 7.9%; $p < 0.001$) (Rohayem et al., 2011). Based on this results it can be presumed that affected individuals may experience more frequent episodes of hypoglycemia, including severe hypoglycemia (Iafusco et al., 2022; Rohayem et al., 2011).

2. Current treatment of diabetes in Wolfram syndrome.

Current DMWS therapy is focused on exogenous insulin replacement using fast and long-acting analogs. However, the individuals with WS may benefit from continuous subcutaneous insulin infusion (CSII) and tight metabolic control. In a case report by M. Cardona et al. 2 siblings with typical early clinical manifestations of WS are presented. A 25-year-old and 22-year-old men with a multiple daily injections (MDI) insulin therapy developed metabolically unstable diabetes requiring therapy modifications. The first case was treated with sensor-augmented insulin infusion system, and the second with an insulin pump. In both cases a decrease of HbA1c values has been observed, from 10.2% (88 mmol/mol) to 7.4% (57 mmol/mol) and 13% (119 mmol/mol) to 7.3% (56 mmol/mol) respectively in 2 years after initialization of insulin therapy in the form of a personal insulin pump (Cardona et al., 2023).

The therapy is also supported by an automatically adjusting insulin delivery device along with continuous glucose monitoring (CGM) sensors which very often operates in a closed-loop system, allowing

for much better results in balancing glycemia levels. The CGM devices allow to the real-time prediction of future glucose levels and enable detection of glycemic episodes including hipo- and hyperglycemia. This allows the patient to respond promptly to changing blood glucose levels and protects him from further deterioration of glycemia (Powers, 2021). Furthermore, in the age of artificial intelligence, potential of personalized algorithms used in hybrid insulin pumps rises significantly creating favorable conditions for modifying improving insulin replacement therapy (Guan et al., 2023).

3. GLP-1 receptor agonists.

As stated before, mutation in the *WFS1* gene is responsible for elevation of ER stress consequently the development of WS (Liiv et al., 2024). Glucagon-like peptide-1 receptor agonists (GLP-1RA) have demonstrated a major therapeutic potential in the treatment of WS and WS-like syndromes, whose common pathogenic feature is loss of endoplasmic reticulum function and impaired calcium transport. Glucagon-like peptide (GLP), an intestinal secreted peptide from L cells performs several key functions, including decreasing ER stress mediated beta-cell apoptosis. Activation of the PERK-ATF4 pathway (Protein kinase RNA-like endoplasmic reticulum kinase and Activating transcription factor 4) also contributes to increasing the regeneration and survival of pancreatic beta cells (Pallotta et al., 2019). For this reason, GLP-1RA are increasingly recommended for use in the adjunctive therapy of DM1 (W. Wang et al., 2017). Furthermore, GLP-1RA's anti-inflammatory and antioxidative properties, as well as augmentative effect of insulin secrecy, proliferation of beta cells and decrease of glucagon secretion, may benefit patients with delay in the progression of micro- and macrovascular diabetes complications (Png et al., 2023). GLP-1RA's by alleviation of ER stress in islet beta cells may also influence preventing the development of diabetes, which in the case of WS would be beneficial for the patient's life quality (Li et al., 2023). In one study an improvement of glycemic metabolic control after inclusion long lasting GLP-1AR liraglutide in the DMWS treatment was observed. It has shown that liraglutide reduce the daily insulin requirement by 20%. Also, 16-week liraglutide administration has shown 4-week transient improvement of glucose toleration (Kondo et al., 2018). Moreover, in case report with autosomal dominant WFS1-related disorder, patient's response to GLP1-RA resulted in better glycemic control and discontinuation of insulin therapy in favor of GLP1-RA (Scully & Wolfsdorf, 2020). Another study conducted on aged WFS1-deficient rats with a long-term therapy of liraglutide showed a neuroprotective effect by reducing neuronal inflammation and alleviating ER stress in the inferior olive. The results suggest that liraglutide is a promising agent to not only treat DMWS but also has potential in reducing neurodegeneration process in WFS1-deficient rats so it may have similar properties in treatment human WS patients (Seppa et al., 2019).

4. Cell regenerative therapy.

As described before, the consequence of the immunological process directed against the body's own beta cells is their atrophy and loss of function, which is secretion of insulin. Currently, numerous studies are underway on the use of induced pluripotent stem cells (iPS) to stop and reverse the process of pancreatic beta cell destruction. The iPS are a type of pluripotent stem cells which can be obtained directly from a somatic cell, for example using patients' skin cells (Urano, 2016). They have ability to multiply indefinitely and can give rise to many types of cells, such as pancreatic and liver cells which gives significant opportunities to transplantology including beta cell transplantation in diabetes (Okita, 2011), (Flatt et al., 2020). Two types of cell regenerative therapy for the pancreas include the process of transplantation and transdifferentiation. The limitation of donor pancreatic beta cell transplantation is their finite number. Therefore, the pluripotent iPS unlock significant opportunities, enabling produce of insulin-secreting cells and then possibility to transplant them (Powers, 2021). Similar effects can be achieved by differentiation of other pancreatic cells such as alfa cells, duct cells and exocrine cells into insulin-secreting cells (Powers, 2021). Better results after transplantation may be obtained if the profile of the pancreatic islet donor is as follows: age between 20 to 50 years old, BMI > 30 kg/m^2, normoglycemia. This is explained by the fact that this clinical profile of donor is associated with the presence of higher quantity of pancreatic islets (measured by IEQ – islet equivalency), and the main goal of the therapy is to use at least 5.000 to 10.000 islet equivalents per kilogram of body weight to improve the effectiveness of the transplantation process (Mohamed et al., 2024).

A recently published case report presents a 59-year-old woman diagnosed with DM1 in 1976 (at the age of 17). In 2012, she was qualified for pancreatic islet transplantation due to diabetes-related complications and unstable glycemic control: intraday glucose fluctuations (50 to 400 mg/dl), HbA1c 7.6% and frequent episodes of symptomatic hypoglycemia (3–4/month). She underwent first islet transplantation (IEQ 346725; IEQ/kg 5592) on March 8, 2014, followed by a second one 4 months later on July 3, 2014 (IEQ 246967;

IEQ/kg 3983). During the 10-year follow-up, significant improvement in glycemic control was observed, allowing the patient to reduce her daily insulin requirement, also the frequency of hypoglycemia decreased. In 2019 she began experiencing deterioration in her neurological function, leading to the suspicion of Wolfram syndrome. Laboratory tests confirmed the absence of antibodies (anti-GAD, anti-IA2, anti-insulin, anti-ZNT8). Genetic test was performed which came out with a positive result, she was found to be a heterozygous carrier of the c.1839G>A, p.Trp613* (ENST00000503569.1) variant in the WFS1 gene (Catarinella et al., 2025). This case report provides evidence of the use of islet transplantation therapy in non-autoimmune diabetes. It demonstrates that metabolic improvement can be achieved in patients with DMWS and other types of diabetes. It also suggests that beta cell regenerative therapy, offering long-term metabolic benefits, could become the next viable treatment option for patients with DMWS and similar conditions.

Discussion:

In this systematic review we describe the clinical characteristics of Wolfram syndrome 1, an autosomal recessive inherited syndrome caused by mutation in the *WFS1* gene. We provide the integrated overview of diabetes mellitus in Wolfram syndrome, focusing on clinical differences between DMWS and type 1 diabetes mellitus. In patients with WS, unlike DM1, rarer ketoacidosis, longer remission periods, better metabolic control, lower daily requirements of insulin, as well as more frequent episodes of hypoglycemia are often observed. This highlights the importance of an early identification and diagnose of WS as the metabolic control and management of the DMWS differs from other forms of diabetes and patients may be misdiagnosed with DM1.

In this article, we also overview the current methods of managing as well as therapeutic advances in treatment of diabetes in Wolfram syndrome. We described strategy of GLP1 receptor agonist use which attempts to reduce ER stress to improve survival of pancreatic beta cells. Studies show overall improvement of metabolic control when GLP1RA are added as an adjunctive therapy. In some cases, glycemic control was sufficiently good to allow insulin therapy to be discontinued. However, much more modern forms of therapy are being examined. Pancreatic beta cell replacement primarily aimed to DM1 therapy, in recent years gained high interest in WS-like disorders, monogenic disorders and insulin-deficient diabetes. Although the progressive cell-based insulin delivery (including both transplantation and transdifferentiation) shows promising properties in regulation of glucose metabolism in patients with diabetes, both DM1 and DMWS, still requires thorough testing. Furthermore, life expectancy in WS is also significantly shorter than in other forms of diabetes. For that reason, it is important to extend the quality of life (QoL) and the expected life span of patients with WS. Currently, to preserve beta cells and proliferate existing ones, mesencephalic astrocyte-derived neurotrophic factor (MANF) is being studied.

In our opinion, further research should focus on investigating methods of early identification patients with WS in addition to testing new and existing drug approaches including GLP-1RA. Recent advances in genetics and transplantology open new possible therapeutic approaches to preserve pancreatic beta cells, thus slowing the progression of diabetes and its complications.

Conclusions:

Wolfram syndrome 1 is a rare disorder characterized by insulin-dependent non-autoimmune diabetes mellitus with an early onset, which is a part of the DIDMOAD acronym. The typical clinical picture of diabetes in WS includes rarer ketoacidosis, longer remission periods, better metabolic control, lower daily requirements of insulin and more frequent episodes of hypoglycemia. The first line treatment at the onset of diabetes in Wolfram syndrome is still insulin. The GLP-1 receptor agonists show promising properties in alleviating endoplasmic reticulum stress and may therefore become a leading therapy for DMWS in the future. Studies suggest that the progressive cell-based insulin delivery therapies may be considered as a treatment for patients with WS, but thorough testing is still required.

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