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THERAPEUTIC APPROACHES IN TYPE 2 DIABETES MELLITUS: ADVANCES AND CLINICAL CHALLENGES

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ABSTRACT

INTRODUCTION: Type 2 diabetes mellitus (T2DM) represents a chronic and progressive condition that affects an increasing proportion of the global population. Its prevalence has risen substantially, driven by factors such as population aging, urbanization, poor diet, and sedentary lifestyle, leading to an increasing burden on healthcare systems. The relationship between obesity and T2DM is well-documented, as obesity amplifies genetic susceptibility and environmental factors, contributing to insulin resistance, a key feature of T2DM pathogenesis (RUZE et al., 2023). Additionally, the ectopic expansion of adipose tissue and the accumulation of certain nutrients and metabolites impair metabolic balance, exacerbating immune-metabolic dysregulation and accelerating the functional loss of β-cells, culminating in elevated blood glucose levels (RUZE et al., 2023).

Keywords: Type 2 Diabetes Mellitus, Therapeutic Approaches, Advances and Challenges.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a chronic and progressive condition that affects an increasing proportion of the global population. Its prevalence has risen substantially, driven by factors such as population aging, urbanization, poor diet, and sedentary lifestyle, leading to an increasing burden on healthcare systems. The relationship between obesity and T2DM is well-documented, as obesity amplifies genetic susceptibility and environmental factors, contributing to insulin resistance, a key feature of T2DM pathogenesis (RUZE et al., 2023). Additionally, the ectopic expansion of adipose tissue and the accumulation of certain nutrients and metabolites impair metabolic balance, exacerbating immune-metabolic dysregulation and accelerating the functional loss of β-cells, culminating in elevated blood glucose levels (RUZE et al., 2023).

T2DM is diagnosed based on the detection of elevated plasma glucose concentrations or hemoglobin A1c (HbA1c) levels in the blood (SACKS et al., 2023). Glycemic control is a key aspect of disease management, monitored primarily through home blood glucose measurements and/or continuous glucose monitoring (CGM) devices, as well as laboratory analysis of HbA1c (SACKS et al., 2023). Moreover, various biomarkers have been investigated as potential auxiliary tools in T2DM management, including the measurement of ketones, autoantibodies, and specific peptides, though many are not recommended for routine clinical practice (SACKS et al., 2023).

Regarding pharmacological treatment, a variety of medications have been used in T2DM management. Metformin, acarbose, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are among the most commonly prescribed drugs, each with distinct mechanisms of action. Metformin, for example, improves insulin sensitivity, while acarbose slows intestinal carbohydrate absorption (SHINTANI; SHINTANI, 2020). SGLT2 inhibitors promote glucose excretion through urine and have been highlighted not only for their glycemic control ability but also for their cardiovascular and renal benefits (SHINTANI; SHINTANI, 2020). These medications have shown the potential to improve not only blood glucose levels but also the longevity of T2DM patients, emphasizing their importance in long-term treatment.

However, the available treatments face significant challenges. Insulin resistance, a core feature of T2DM, is not always fully controlled with current therapies, and disease progression can result in microvascular and macrovascular complications. Additionally, the interactions between T2DM treatments and obesity, such as anti-obesity drug therapies

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that also target T2DM, highlight the complexity of managing these conditions (RUZE et al., 2023). Bariatric surgery has proven to be an effective treatment for patients with T2DM and obesity, offering significant benefits in terms of glycemic control and weight loss (RUZE et al., 2023).

Therefore, T2DM therapeutic approaches are multifaceted, involving lifestyle modifications as well as pharmacological and surgical interventions. While several therapeutic options exist, many challenges remain, requiring ongoing research into the disease's pathogenesis and the development of new treatments. This article aims to explore current therapeutic approaches for T2DM, highlighting advances and clinical challenges faced in managing this complex condition.

METHODOLOGY

This study is a literature review aimed at synthesizing the most recent information on therapeutic approaches in the treatment of Type 2 Diabetes Mellitus (T2DM), highlighting advances and clinical challenges. The search was conducted in the PubMed database, including articles published between 2019 and 2024, using the descriptors “Diabetes Mellitus” and “Treatment.” Original studies, reviews, and meta-analyses published exclusively in English and available in full text were selected.

Inclusion criteria encompassed studies addressing pharmacological, non-pharmacological, and combined therapies, while exclusion criteria excluded articles outside the specified period, not available in full text, or irrelevant to the topic. Study selection followed a two-phase process: search and screening of titles and abstracts, followed by full reading of the selected articles.

Data analysis was qualitative, organizing studies according to the types of therapies discussed. The methodology was conducted systematically, ensuring transparency and reproducibility, based on high-quality peer-reviewed sources.

RESULTS AND DISCUSSION

Type 2 Diabetes Mellitus (T2DM) represents one of the most prevalent and complex conditions in the global health landscape. Its management has significantly evolved with the introduction of new therapies that aim not only to control glycemic levels but also to minimize the complications associated with the disease. Among the most innovative therapeutic alternatives, stem cell approaches and islet transplants stand out, aiming to

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restore the endocrine function of the pancreas. Pancreatic cell transplantation, especially islet transplantation, has shown promising results, allowing the restoration of insulin secretion in T2DM patients. However, this approach faces significant limitations. Among the challenges are the high rate of graft rejection, adverse effects associated with the necessary immunosuppression, and the scarcity of islet donors. These difficulties highlight the need for innovations to improve the efficacy and durability of transplants. Furthermore, recent studies have explored the use of induced pluripotent stem cells to generate beta cells, an alternative that may overcome the limitations of traditional transplants, although there are still risks related to teratoma formation and the safety of their clinical application (ARAKI, 2024; FERGUSON; FINCK, 2021).

In addition to transplants, mesenchymal stem cells (MSCs) have attracted significant interest due to their regenerative potential. MSCs derived from various sources, including the umbilical cord, have shown efficacy in treating microvascular and macrovascular complications of T2DM, such as diabetic neuropathy, retinopathy, and diabetic ulcers. Experimental and clinical studies have demonstrated that the infusion of these cells can improve insulin resistance and help regenerate damaged tissues, promoting reduced inflammation and improved vascular function. However, the clinical application of MSCs still faces challenges, including low cell survival rates after infusion and the risk of complications such as thrombosis and tumor development. The enhancement of cell culture techniques and the use of genetic engineering strategies, such as CRISPR/Cas9, have been explored to increase the efficacy and safety of MSCs in T2DM treatment (ARAKI, 2024; SUN et al., 2021).

In the pharmacological field, the use of medications for glycemic control continues to be the cornerstone of T2DM therapeutic approaches. Metformin, for example, is widely recommended as a first-line treatment due to its proven benefits, such as reducing hepatic gluconeogenesis and improving insulin sensitivity. However, metformin is not without side effects, such as gastrointestinal disturbances and the rare possibility of lactic acidosis. Additionally, its efficacy may be limited in patients with renal insufficiency or the elderly. Acarbose, another medication used in T2DM control, acts by reducing carbohydrate absorption in the gastrointestinal tract, delaying the rise in postprandial glucose levels. Besides controlling glucose, acarbose has shown beneficial effects in preventing the progression of glucose tolerance to T2DM. Although effective, this drug may be associated

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with gastrointestinal side effects such as flatulence and abdominal bloating (ARAKI, 2024; FERGUSON; FINCK, 2021).

GLP-1 antagonists represent a class of drugs that have gained prominence in T2DM treatment. Medications such as liraglutide, exenatide, and semaglutide have proven effective in reducing blood glucose levels, promoting glucose-dependent insulin secretion, and reducing glucagon production, a hormone that raises glucose levels. Additionally, these drugs have been associated with weight loss, an added benefit for many T2DM patients who often have obesity. The reduction of hepatic steatosis and improvement in liver function, particularly in patients with NASH (non-alcoholic steatohepatitis), have also been observed. Although this drug class has a relatively good safety profile, side effects such as nausea, diarrhea, and abdominal pain may occur. Recent studies have indicated that GLP-1 agonists also have a positive impact on reducing hepatic inflammation markers and fibrosis, making them a promising therapeutic option for patients with liver complications associated with T2DM (FERGUSON; FINCK, 2021; SHINTANI; SHINTANI, 2020).

Beyond pharmacological and cellular therapies, nutritional management plays a crucial role in T2DM control. Specifically, implementing dietary strategies based on a balanced diet with an emphasis on low glycemic index foods has shown substantial benefits in glycemic control and preventing long-term complications. The dietary approach should be personalized for each patient, considering their clinical conditions, age, and risk factors. Elderly patients, in particular, may face additional challenges such as malnutrition, which exacerbates glycemic control and increases the risk of complications associated with T2DM. The ideal treatment should combine pharmacological therapies with a rigorous nutritional approach that promotes glycemic control without compromising the patient's nutritional status (ARAKI, 2024; SHINTANI; SHINTANI, 2020).

Finally, it is important to highlight that despite significant advances in T2DM treatment, considerable challenges remain. The efficacy and safety of emerging therapies, such as the use of stem cells and GLP-1 therapies, need to be evaluated in larger, long-term clinical studies. The integration of pharmacological strategies, cellular therapies, and nutritional interventions remains an area of intense research and development, aimed at improving glycemic control and minimizing long-term complications of T2DM. Continuous patient monitoring and personalized treatment remain crucial for long-term therapeutic success.

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CONCLUSION

Type 2 Diabetes Mellitus (T2DM) continues to be one of the greatest public health challenges worldwide, with increasing prevalence and a significant impact on patients' quality of life. Therapeutic approaches for disease control have evolved significantly, particularly with the use of medications, cellular therapies, and nutritional strategies. The combination of drugs such as metformin, acarbose, and GLP-1 antagonists has proven effective in glycemic control, along with additional benefits such as weight loss reduction and improvement in associated complications like hepatic steatosis and diabetic neuropathy. However, the limitations and adverse effects of these treatments still represent challenges, requiring the continuous search for more effective and safe therapeutic alternatives.

Cellular therapies, including the use of stem cells and islet transplants, offer enormous regenerative potential, with promising results in restoring pancreatic function and controlling glycemia. However, challenges related to immune rejection and the safety of these therapies still need to be overcome before their large-scale clinical application. Mesenchymal stem cells (MSCs) emerge as a promising alternative, mainly due to their anti-inflammatory and regenerative potential, offering significant benefits in reversing the microvascular and macrovascular complications of T2DM.

Implementing adequate nutritional interventions, with an emphasis on a low-glycemic diet, is an essential component in managing T2DM, especially in patients with additional risk factors like obesity and old age. Personalizing treatment, combining pharmacological strategies, cellular therapies, and lifestyle modifications, remains critical for success in disease control and preventing long-term complications.

In conclusion, although therapeutic advances have significantly improved T2DM management, challenges related to long-term efficacy, safety, and patient adherence remain. The future of T2DM treatment will depend on the continued integration of new therapeutic approaches, including emerging technologies, and the personalization of care based on individual patient needs. The development of new therapies and the refinement of current approaches are crucial to achieving effective and sustainable glycemic control, improving quality of life, and reducing the impact of disease complications.

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