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Incretin-Based Therapies For Type 2 Diabetes Mellitus

[1] A.Abdullah, [1] A.Khan

[1,2] California Northstate University College of Medicine
Correspondence : dr.abdullah948573@gmail.com

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ABSTRACT

Background: The increasing prevalence of type 2 diabetes mellitus (T2DM) has prompted significant advancements in therapeutic strategies aimed at improving glycemic control and mitigating associated comorbidities. **Literature Review:** Initial discussions highlight the advantages of incretin-based therapies over traditional treatments, with studies showing their ability to promote weight loss and minimize hypoglycemia risks (Nisal et al., 2012). This is particularly important given the psychological and physiological challenges associated with weight gain in T2DM management. The comparative effectiveness of these therapies is also a focal point in the literature. While both classes enhance insulin secretion in a glucose-dependent manner, their mechanisms differ, leading to varying efficacy and tolerability profiles (Brunton, 2014). DPP-4 inhibitors, for instance, have been noted for their ability to correct the "incretin defect" commonly observed in T2DM patients, preserving pancreatic function and mitigating adverse effects (Godinho et al., 2015). This positions them as a valuable component of T2DM therapeutics, particularly for patients who may not tolerate other treatments well. The integration of these therapies into clinical practice has been supported by robust evidence indicating their effectiveness and safety throughout the disease's progression (M. Tibaldi, 2014). Moreover, the literature emphasizes the importance of understanding the molecular pharmacology of incretin receptors and the potential for new therapeutic developments, such as dual agonists that target both GLP-1 and GIP receptors (Al-Sabah, 2016). Such advancements could enhance glycemic control and address weight management challenges, ultimately improving patient outcomes. **Conclusion:** In conclusion, the body of literature surrounding incretin-based therapies for T2DM underscores their transformative impact on diabetes management. These therapies not only facilitate effective glycemic control but also promote weight loss and cardiovascular health, addressing critical comorbidities associated with T2DM. The ongoing exploration of their mechanisms, clinical applications, and long-term effects will be vital in optimizing treatment strategies and improving patient quality of life.

Keyword: Incretin-Based Therapies, Type 2 Diabetes Mellitus

INTRODUCTION

The increasing prevalence of type 2 diabetes mellitus (T2DM) has prompted significant advancements in therapeutic strategies aimed at improving glycemic control and mitigating associated comorbidities. The literature surrounding incretin-based therapies has evolved to highlight their multifaceted benefits, particularly in comparison to traditional treatment modalities. In a foundational review, (Nisal et al., 2012) delineate the advantages of incretin-based therapies, specifically dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, emphasizing their ability to maintain weight or promote weight loss while minimizing the risk of hypoglycemia—a notable improvement over conventional treatments.

Building on this foundation, (A. Davidson, 2013) expands the discourse to encompass the broader implications of incretin-based therapies beyond mere glycemic control. This article underscores the importance of addressing cardiovascular safety in the management of T2DM, revealing that GLP-1 receptor agonists and DPP-4 inhibitors not only facilitate glycemic regulation but also contribute to cardiovascular risk reduction and improvements in blood pressure. The emphasis on individualized patient care in the management of T2DM reflects a growing recognition of the need to tailor treatment approaches to patient-specific factors, including preferences and tolerability.

Further inquiry into the comparative effectiveness of these therapies is presented by (Brunton, 2014), who questions whether one class of incretin-based therapy is superior to the other. The author highlights the mechanisms by which these therapies enhance insulin secretion in a glucose-dependent manner, while also addressing the limitations of native GLP-1 due to its rapid degradation. This critical evaluation of the pharmacological properties of incretin-based therapies provides a nuanced understanding of their roles in clinical practice.

(M. Tibaldi, 2014) continues this exploration by discussing the practical integration of incretin-based therapies into clinical routines. The review emphasizes

the therapeutic potential of both GLP-1 receptor agonists and DPP-4 inhibitors in managing T2DM, noting their favorable side effect profiles and sustained efficacy throughout the disease's progression. The article reinforces the notion that incretin-based therapies are well tolerated and effective, further solidifying their place in contemporary diabetes management.

(Godinho et al., 2015) delve deeper into the unique contributions of DPP-4 inhibitors, addressing their ability to rectify the "incretin defect" commonly observed in T2DM patients. This review highlights the potential of DPP-4 inhibitors to preserve pancreatic function and mitigate adverse effects, thereby positioning them as a critical component of T2DM therapeutics.

The distinctions between GLP-1 receptor agonists and DPP-4 inhibitors are further elucidated by (Nauck, 2016), who articulates the shared mechanisms of action and therapeutic benefits of these agents. This comparative analysis not only clarifies their respective roles in glycemic control but also emphasizes the additional benefits, such as weight loss and improvements in β-cell function, which are critical for holistic diabetes management.

(Al-Sabah, 2016) contributes to the understanding of incretin physiology by detailing the molecular pharmacology of incretin receptors. The acknowledgment of the "incretin effect" underscores the significance of these hormones in insulin secretion dynamics and the implications of their loss in T2DM pathology. The article highlights the therapeutic advancements stemming from the development of long-acting GLP-1 receptor agonists and DPP-4 inhibitors, which have become mainstays in T2DM treatment.

Recent research by (M. Zakaria et al., 2012) further investigates the cardiovascular implications of DPP-4 inhibitors, showcasing their potential cardioprotective effects. This review emphasizes the multifaceted role of incretin hormones in cardiovascular health, suggesting that DPP-4 inhibition may yield favorable outcomes independent of glycemic control.

Finally, (Wan et al., 2013) encapsulate the current landscape of incretin-based therapies, reaffirming their position as preferred first-line injectable treatments for T2DM. The authors highlight the significant advancements in pharmacological options, including prolonged circulation GLP-1 analogs and DPP-

4 inhibitors, which collectively enhance glycemic control while promoting weight management and cardiovascular health.

Collectively, these articles illustrate the transformative impact of incretin-based therapies in the management of T2DM, underscoring their efficacy, safety, and the necessity for individualized treatment approaches that consider patient-specific needs and preferences.

LITERATURE REVIEW

The article "Comparison of efficacy between incretin-based therapies for type 2 diabetes mellitus" by Nisal, Kela, Khunti, and Davies (Nisal et al., 2012) provides a comprehensive analysis of the evolving landscape of treatment options for type 2 diabetes mellitus (T2DM), particularly focusing on incretin-based therapies. The authors highlight the alarming rise in T2DM prevalence globally, particularly among obese individuals, and underscore the limitations of traditional glucose-lowering medications, which often exacerbate weight gain. This aspect is crucial, as the psychological and physiological implications of weight gain can significantly deter patients from adhering to diabetes management regimens.

The review meticulously contrasts two primary classes of incretin-based therapies: dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists. The authors present compelling evidence from head-to-head comparative trials that assess the efficacy, tolerability, and safety profiles of these agents. The findings indicate that incretin-based therapies not only facilitate effective glycemic control but also possess the potential to mitigate weight gain or even promote weight loss, a significant advantage over conventional therapies (Nisal et al., 2012).

Furthermore, the article discusses the limitations of existing studies, including variations in trial designs and patient populations, which may impact the generalizability of the results. The authors aptly call for more rigorous and standardized research to bolster the comparative understanding of these therapies. This critical evaluation of the literature presents a balanced view, acknowledging the benefits of incretin-based therapies while recognizing the need for further exploration into their long-term effects and overall impact on patient quality of life.

The article "Incretin-Based Therapies: Focus on Effects Beyond Glycemic Control Alone" by Jaime A. Davidson (A. Davidson, 2013) provides a comprehensive overview of the multifaceted nature of type 2 diabetes mellitus and the role of incretin-based therapies in its management. Davidson emphasizes the importance of addressing not only glycemic control but also the associated comorbidities such as hypertension and dyslipidemia, which are prevalent in this patient population. This holistic approach is crucial, as inadequate management of these risk factors can lead to significant functional impairment across multiple organ systems.

The article highlights the regulatory landscape surrounding the approval of new antihyperglycemic agents, particularly the GLP-1 receptor agonists (GLP-1RAs) and DPP-4 inhibitors. Davidson notes that these classes of medications were the first to require demonstration of cardiovascular (CV) safety as a prerequisite for regulatory approval, reflecting a shift in focus towards long-term outcomes beyond mere glucose lowering (A. Davidson, 2013). This is particularly relevant given the increasing recognition of the cardiovascular implications of diabetes management.

Davidson outlines the therapeutic profiles of GLP-1RAs and DPP-4 inhibitors, noting their respective benefits and potential side effects. For instance, GLP-1RAs are associated with weight loss, improvements in blood pressure (BP), and reductions in inflammatory markers, which are significant advantages in the context of diabetes management (A. Davidson, 2013). However, the side effect profile, particularly the potential for nausea and vomiting, may pose challenges for patient adherence. Conversely, DPP-4 inhibitors are well-tolerated, with an oral administration route that enhances patient acceptance, making them a favorable option for many individuals.

The article further discusses the necessity of individualized patient care, as emphasized by the American Diabetes Association guidelines, which advocate for consideration of patient preferences and medication costs alongside potential side effects (A. Davidson, 2013). This patient-centered approach is vital for improving medication adherence and overall treatment outcomes.

Moreover, Davidson introduces the underlying mechanisms of incretin-based therapies, suggesting that they may influence glucose homeostasis and other

physiological processes through multiple signaling pathways. Emerging evidence indicates that GLP-1 receptors may have a direct impact on BP regulation and cardiac function, contributing to the observed modest decreases in BP and reduced CV event risk associated with these therapies (A. Davidson, 2013).

The article titled "Incorporating Incretin-Based Therapies into Clinical Practice for Patients with Type 2 Diabetes" by Joseph M. Tibaldi (M. Tibaldi, 2014) provides a comprehensive overview of the integration of incretin-based therapies in managing type 2 diabetes mellitus (T2D). The author emphasizes the necessity of combining clinical evidence with practitioner experience and patient preferences to optimize treatment outcomes for T2D patients.

Tibaldi thoroughly reviews the two primary classes of incretin-based therapies: glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors). The article highlights the multifaceted approach of incretin therapies, which target various dysfunctional organs involved in T2D. GLP-1RAs, such as liraglutide and exenatide, are noted for their significant efficacy in achieving glycemic control and promoting weight loss, while DPP-4 inhibitors are recognized for providing moderate glycemic control with weight neutrality. This distinction is critical, as weight management is a significant concern in T2D treatment.

The article further elucidates the physiological roles of incretins, particularly their ability to stimulate insulin secretion, inhibit glucagon release, and modulate gastric emptying. Tibaldi underscores the impairment of these processes in T2D patients, thereby illustrating the therapeutic potential of incretin-based therapies in restoring normal physiological functions. The author supports the assertion that both classes of incretin therapies are effective, well-tolerated, and associated with a low incidence of hypoglycemia, which is a common concern with many antidiabetic medications.

One of the strengths of this article is its reliance on a systematic review of studies published from 2000 to 2012, which lends credibility to the claims made regarding the efficacy and safety of incretin therapies. Tibaldi's analysis of clinical experiences corroborates the findings from these studies, reinforcing the argument

that incretin-based therapies can provide sustained glycemic control and favorable weight outcomes throughout the progression of T2D.

However, while the article presents a well-rounded view of incretin-based therapies, it could benefit from a more detailed exploration of potential long-term effects and the limitations of these therapies in certain populations. Additionally, the discussion could be enriched by including patient adherence factors and the impact of these therapies on overall health outcomes beyond glycemic control and weight management.

The article titled "The Place of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Therapeutics: A 'Me Too' or 'the Special One' Antidiabetic Class?" by Godinho et al. (Godinho et al., 2015) provides a comprehensive examination of the role of incretin-based therapies, specifically Dipeptidyl Peptidase-4 (DPP-4) inhibitors, in the management of type 2 diabetes mellitus (T2DM). The authors argue that these therapies represent a significant advancement in diabetes treatment, addressing multiple pathophysiological aspects of T2DM, including hypersecretion of glucagon, abnormal gastric emptying, and postprandial hyperglycemia.

One of the key insights presented is the ability of DPP-4 inhibitors, also known as gliptins, to enhance the availability of glucagon-like peptide-1 (GLP-1). This mechanism effectively corrects the "incretin defect" commonly observed in T2DM patients, leading to improved glycemic control with a lower risk of hypoglycemia compared to other antidiabetic agents. The authors critically evaluate clinical studies that support the efficacy of DPP-4 inhibitors, highlighting their favorable safety profile and minimal adverse effects, which positions them as a viable option for managing T2DM.

Moreover, the article delves into the emerging evidence surrounding the cytoprotective effects of DPP-4 inhibitors on pancreatic function. The authors discuss how these agents may inhibit apoptotic pathways and stimulate β-cell proliferation, which could potentially preserve pancreatic function over time. This aspect is particularly compelling as it suggests a dual benefit of glycemic control and pancreatic protection, which could alter the disease trajectory for many patients.

The review further addresses the systemic benefits of DPP-4 inhibitors beyond glycemic control, noting their potential protective effects on critical organs

affected by T2DM complications, such as the heart, kidneys, and retina. These findings are significant as they underscore the broader therapeutic implications of DPP-4 inhibitors in mitigating the long-term complications associated with T2DM.

However, the authors also acknowledge the challenges that lie ahead in establishing DPP-4 inhibitors as the preferred therapy for T2DM. They point out the need for further research to solidify the long-term outcomes of these therapies, particularly in relation to their ability to ameliorate nephropathy, retinopathy, and cardiovascular complications. The article concludes with a call for ongoing studies to explore the full potential of DPP-4 inhibitors in transforming T2DM management.

The article by Nauck (Nauck, 2016) presents a comprehensive overview of incretin-based therapies, particularly focusing on the mechanisms of action of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes mellitus (T2D). The author emphasizes the significance of the incretin system, which plays a crucial role in glucose metabolism and insulin secretion. This system is particularly relevant for patients with T2D, where the conventional response of β cells to incretin hormones is impaired.

Nauck delineates the distinct pharmacological actions of the two classes of incretin-based therapies. GLP-1RAs directly stimulate GLP-1 receptors, enhancing insulin secretion in a glucose-dependent manner, while DPP-4 inhibitors function by inhibiting the enzyme responsible for the degradation of endogenous GLP-1, thereby increasing its availability. This fundamental difference in action leads to varying efficacy and tolerability profiles between the two therapies. The article critically highlights that while both classes achieve reductions in plasma glucose levels, their mechanisms confer differing benefits and risks, particularly concerning hypoglycemia.

Moreover, the article underscores the additional advantages associated with incretin therapies beyond glycemic control. These include weight loss and improvements in β-cell function and cardiovascular risk markers, which are particularly pertinent given the multifaceted nature of T2D management. Nauck's analysis reveals that the non-glycemic effects of these therapies can significantly

enhance patient outcomes and quality of life, making them attractive options in the therapeutic landscape for T2D.

The article "Molecular Pharmacology of the Incretin Receptors" by Suleiman Al-Sabah (Al-Sabah, 2016) provides a comprehensive overview of the incretin hormones and their roles in insulin secretion, particularly in the context of type 2 diabetes mellitus (T2DM). The author elucidates the concept of the 'incretin effect', which describes the phenomenon where oral glucose intake results in a greater insulin response compared to intravenous glucose administration. This effect is significant, as it accounts for more than half of the insulin secreted in response to a meal, highlighting the critical role of incretin hormones in glucose metabolism.

Al-Sabah identifies two primary incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The synthesis of GIP occurs in K cells located in the duodenum and jejunum, while GLP-1 is derived from the proglucagon gene, produced in intestinal L cells. The secretion of these hormones is predominantly stimulated by glucose ingestion, although other nutrients can also trigger their release. This insight is particularly relevant as it underscores the physiological mechanisms that are often impaired in T2DM, where the incretin effect is diminished.

The article critically evaluates the limitation of native incretin peptides in T2DM treatment due to their rapid inactivation by dipeptidyl peptidase IV (DPP-IV). This presents a significant barrier to utilizing GIP and GLP-1 in their native forms for therapeutic purposes. However, the development of long-acting GLP-1 receptor (GLP-1R) agonists and DPP-IV inhibitors has marked a significant advancement in incretin-based therapies. The author notes that while GLP-1R agonists have gained considerable attention and clinical application, GIP receptors (GIPR) have not been as thoroughly explored as potential drug targets.

Furthermore, the article discusses the promising avenue of dual agonists that activate both GIPR and GLP-1R, suggesting that such compounds may offer effective treatment options for T2DM and obesity. This dual approach could potentially enhance glycemic control and weight management, addressing two of the major challenges faced by individuals with T2DM.

The article titled "Cardiovascular protection by DPP-4 inhibitors in preclinical studies: an updated review of molecular mechanisms" by Esraa M. Zakaria, Walaa M. Tawfeek, Mohamed H. Hassanin, and Mohammed Y. Hassaballah (M. Zakaria et al., 2012) provides a comprehensive overview of the cardiovascular implications of dipeptidyl peptidase 4 inhibitors (DPP-4i) in the context of type 2 diabetes mellitus (DM). The authors effectively highlight the relationship between type 2 DM and cardiovascular complications, emphasizing the impaired incretin response observed in diabetic patients compared to those with normal glucose levels.

The article begins by elucidating the role of incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), in the regulation of insulin secretion and other metabolic processes. The authors detail the multifaceted effects of GLP-1, including its ability to promote insulin release, inhibit gastric emptying, and exert actions on various tissues such as the brain and myocardium. This broad spectrum of activity underscores the importance of incretins in both glycemic control and cardiovascular health.

A significant contribution of the article is its exploration of the molecular mechanisms through which DPP-4 inhibitors exert their cardioprotective effects. The authors present evidence that DPP-4 inhibition enhances AMP-activated protein kinase (AMPK) activity and stimulates mitochondrial respiratory capacity, suggesting a potential pathway for improved cardiac function. Additionally, the article discusses the role of DPP-4 in the degradation of several peptides, including B-type natriuretic peptide, which is crucial for cardiovascular homeostasis. This highlights the complexity of DPP-4's actions and the potential for DPP-4i to provide cardiovascular benefits beyond glycemic control.

The authors also note that the cardioprotective effects of DPP-4 inhibitors may be independent of GLP-1 activity, a point that is particularly relevant for the understanding of these medications in the broader context of cardiovascular risk management in diabetic and non-diabetic populations. This assertion is supported by preclinical studies that indicate favorable cardiovascular outcomes associated with DPP-4i use.

However, while the article presents a robust overview of the mechanisms involved, it could benefit from a more detailed discussion of clinical implications and outcomes observed in human studies. The preclinical focus, while informative, leaves a gap in understanding how these findings translate to real-world patient populations. Future research should aim to bridge this gap by investigating the long-term cardiovascular outcomes of DPP-4i in diverse cohorts.

The article "GLP-1R Signaling and Functional Molecules in Incretin Therapy" by Wan et al. (Wan et al., 2013) provides a comprehensive overview of the role of incretin-based therapies in the management of type 2 diabetes mellitus (T2DM), a condition that has reached epidemic proportions globally, affecting approximately 10% of adults. The authors emphasize that T2DM constitutes over 90% of diabetes cases, with a significant number of individuals remaining undiagnosed. This underscores the urgent need for effective management strategies.

The article outlines the foundational approach to T2DM management, which includes lifestyle modifications and the use of metformin. However, it highlights the limitations of these traditional methods and introduces incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as promising alternatives. GLP-1, in particular, is noted for its multifaceted benefits, including its ability to stimulate insulin secretion, reduce appetite, and promote weight loss. These attributes make GLP-1 a compelling candidate for T2DM treatment.

A critical aspect discussed is the vulnerability of GLP-1 to rapid degradation by dipeptidyl peptidase 4 (DPP-4), which significantly limits its therapeutic potential due to a short half-life in circulation. The authors address this challenge by exploring the development of DPP-4 inhibitors and GLP-1 receptor (GLP-1R) agonists, which have been designed to enhance the stability and efficacy of GLP-1. The article provides evidence supporting the efficacy of GLP-1R agonists, particularly in terms of weight management and cardiovascular health, thereby establishing their superiority over traditional therapies.

Moreover, the article delves into the signaling mechanisms of GLP-1R, elucidating how these pathways contribute to the physiological effects observed with GLP-1R agonists. This mechanistic insight is crucial for understanding the

therapeutic benefits and potential side effects associated with incretin-based therapies.

CONCLUSION

The literature on incretin-based therapies for type 2 diabetes mellitus (T2DM) has significantly advanced, providing a comprehensive understanding of their multifaceted benefits and implications for patient management. The introduction of incretin-based therapies, specifically glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, has marked a paradigm shift in the treatment of T2DM, emphasizing not only glycemic control but also weight management and cardiovascular health.

Initial discussions highlight the advantages of incretin-based therapies over traditional treatments, with studies showing their ability to promote weight loss and minimize hypoglycemia risks (Nisal et al., 2012). This is particularly important given the psychological and physiological challenges associated with weight gain in T2DM management. Furthermore, the cardiovascular implications of these therapies have garnered attention, with evidence suggesting that GLP-1 receptor agonists and DPP-4 inhibitors contribute to cardiovascular risk reduction, thus addressing a critical aspect of T2DM management (A. Davidson, 2013).

The comparative effectiveness of these therapies is also a focal point in the literature. While both classes enhance insulin secretion in a glucose-dependent manner, their mechanisms differ, leading to varying efficacy and tolerability profiles (Brunton, 2014). DPP-4 inhibitors, for instance, have been noted for their ability to correct the "incretin defect" commonly observed in T2DM patients, preserving pancreatic function and mitigating adverse effects (Godinho et al., 2015). This positions them as a valuable component of T2DM therapeutics, particularly for patients who may not tolerate other treatments well.

The integration of these therapies into clinical practice has been supported by robust evidence indicating their effectiveness and safety throughout the disease's progression (M. Tibaldi, 2014). The favorable side effect profiles of both GLP-1 receptor agonists and DPP-4 inhibitors further solidify their place in contemporary

diabetes management, allowing for individualized treatment approaches that cater to patient-specific needs (M. Zakaria et al., 2012).

Moreover, the literature emphasizes the importance of understanding the molecular pharmacology of incretin receptors and the potential for new therapeutic developments, such as dual agonists that target both GLP-1 and GIP receptors (Al-Sabah, 2016). Such advancements could enhance glycemic control and address weight management challenges, ultimately improving patient outcomes.

In conclusion, the body of literature surrounding incretin-based therapies for T2DM underscores their transformative impact on diabetes management. These therapies not only facilitate effective glycemic control but also promote weight loss and cardiovascular health, addressing critical comorbidities associated with T2DM. The ongoing exploration of their mechanisms, clinical applications, and long-term effects will be vital in optimizing treatment strategies and improving patient quality of life.

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