The Review of DIABETIC STUDIES

EDITORIAL



# The Continuing Need for Drug Development and Clinical Trials in Type 2 Diabetes and its Complications: Introduction to The RDS Special Issue

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## ■ Abstract

The increased burden of type 2 diabetes (T2D) necessitates the need for effective and safe novel drugs to treat this epidemic disease and its complications. By compiling this RDS Special Issue, our aim was to provide a comprehensive and critical overview on recent, ongoing, and future developments in this field. In collaboration with distinguished and renowned experts, we analyzed and discussed the most important advances in the field of incretin-based therapies, their extraglycemic effects, cardiovascular actions, and specific properties of the central nervous system. Another important drug class currently in development, the SGLT-2 inhibitors, and the role of the kidney in T2D are topics also covered by this issue. In addition to drug developments, new physiological insights into the understanding of the organ pathophysiology in T2D are presented that may eventually lead to additional therapeutic targets for obesity, T2D, and chronic inflammation acting on the brain, cardiovascular system, and pancreatic islets. The outcome of this Special Issue is a comprehensive reference work including bundled knowledge and expert opinions on the various aspects of the disease and its possible therapy strategies available now and in the near future. However, despite the advances delivered by modern incretin-based therapies today, there are still many limitations associated with efficacy data, application routes, and safety issues, which prevent the decline in diabetes complication rates. We conclude that further drug development and clinical trials are required to overcome these limitations, and to counteract the movement towards higher incidence rates of T2D and its complications.

**Keywords**: type 2 diabetes · incretin-based therapy · extraglycemic effects · antidiabetic · SGLT-2 inhibitor

## The significance of new therapeutic developments in the treatment of type 2 diabetes and its complications

Type 2 diabetes (T2D) is an increasing global health burden with estimated 350 million affected people and increasing incidence rates [1, 2]. It is among the 5 principal sources of non-infectious diseases in industrialized and developing countries with an estimated global cost of treatment of 47 trillion US dollars [3]. The disease is adversely affecting health, life-expectancy, quality of life, and health care systems. Despite enormous efforts to develop new treatment strategies, more than 50% of patients are not at treatment target and rates for complications and mortality are still high. According to the National Institute of Health (NIH), incidence rates for diabetes complications between 2004 and 2008 in the US were: retinopathy 28.5%, nephropathy 44%, and an estimate of 60-70% with nerve damages [4]. This in-

dicates that ideal and more effective therapeutic measures have not yet been introduced. It is therefore important to develop new strategies for effectively combating T2D so that incidence rates of the disease and its complications are reduced.

A decisive feature of T2D is that different risk factors have different effects on the appearance and course of the disease and its complications. It is thus a multi-factorial disease, and decades of clinical experience have shown that a single unique optimal therapy does not exist. Instead, T2D therapy requires patient-type-related and individual treatment forms based on adjusted algorithms. In addition, it is widely recognized that, in many cases, therapy should include a mixture of various approaches, including lifestyle changes (regarding eating behavior, physical activity, smoking, etc.) to reduce risk factors, and oral or injectable drugs to counteract the pathophysiology of T2D. Optimally, therapy should correct cardiovascular (CV) risk factors, normalize blood glucose levels, and prevent late complications.

**Abbreviations**:
ABCD - age, body weight, complications, disease duration
ACEI - angiotensin converting enzyme inhibitors
ARB - angiotensin receptor blockers
CV - cardiovascular
DPP-4 - dipeptidyl peptidase-4
EMA - European Medicines Agency
ERK1/2 - extracellular signal-regulated kinases 1/2
FA - fatty acid
FDA - Food and Drug Administration
GLP-1 - glucagon-like peptide-1
HbA1c - glycated hemoglobin
MCP-1 - monocyte chemotactic protein-1
NIH - National Institute of Health
Nrf2 - nuclear factor (erythroid-derived 2)-like 2
PI3 - Phosphoinositide-3
PP - pancreatic polypeptide
RDS - Review of Diabetic Studies
SGLT-1/2 - sodium-glucose cotransporter type 1/2
SU - sulphonylureas
T2D - type 2 diabetes
TZD - thiazolidinediones

## Available therapies

Since the advent of incretin-based antidiabetic therapy in clinical practice, drug development has made considerable progress, and shows several advantages over traditional oral antidiabetic drugs (such as sulphonylureas (SU) and thiazolidinediones (TZD)) and insulin. The advantages include hypoglycemic effects with very low risk of hypoglycemia, possibly improved or preserved beta-cell function, and extraglycemic effects (body weight reduction and beneficial effects on cardiovascular risk factors) [5]. Due to the various beneficial effects, these new drugs are also considered for use in prediabetes, as discussed in the article by Alan Garber in this issue [5].

## New therapies based on incretin action - benefits and possible limitations

The existing glucagon-like peptide 1 (GLP-1) agonists (exenatide, liraglutide) or dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin) are established in T2D therapy. They are approved as add-on therapy in combination with metformin, SU, and TZD to take advantage of synergetic effects that include secured glycemic control with minimal episodes of hypoglycemia, which is more frequent in combination with SU and insulin. There are several novel agents of the GLP-1 receptor agonist class and the DPP-4 inhibitors in development. Within the GLP-1 receptor agonist class, recent developments are targeted principally towards longer acting compounds for once weekly dosing or even longer dosing intervals. The effects of incretin-based drugs alone and in combination are mostly beneficial, but research is still ongoing and some safety issues are currently under observation, including pancreatitis and cancer [5].

The full spectrum of effects found in ongoing research is analyzed and discussed in comprehensive reviews published in this RDS Special Issue on T2D treatment and clinical studies. The article by Carolyn Deacon and Bo Ahren examines the physiology of incretins in health and disease by analyzing the modes of action and the pathways initiated by native incretin hormones [6]. The analysis concludes that direct stimulation of the enteroendocrine cells by the presence of nutrients in the intestinal lumen is likely the most important factor in the regulation of human incretin hormone secretion, but that other (neural and hormonal) mechanisms play additional roles. GLP-1 and GIP failure in disease states arise secondarily to insulin resistance, but are critical contributors to disease escalation [6].

We have learned much from results of clinical research on marketed products with direct pharmacological GLP-1 agonist action (the so-called incretin mimetics) or indirect increase in physiological endogenous GLP-1 through inhibition of DPP-4, the enzyme that degrades both GLP-1 and GIP, (the DPP-4 inhibitors). Among the GLP-1 agonists,

two compounds are available; firstly, exenatide (first approved agent by FDA in 2005) followed by liraglutide (approval in 2009). Sitagliptin, vildagliptin, and saxagliptin are the DPP-4 inhibitors, with sitagliptin firstly introduced in 2006. The application of these agents vary at different disease stages. Traditional therapeutic algorithms use oral agents (metformin, SU, TZD) in a stepwise, additive manner when specific targets are not reached. However, this approach does not prevent beta-cell loss, nor does it assure sustainable glycemic control. Using incretin-based agents, a progression from prediabetic states to abnormal glycemic levels may be delayed. In later stages, incretin agents are recommended preferably in combination with metformin and lifestyle interventions, and finally, even in combination with insulin. The benefits of incretin therapy at various stages of diabetes are reviewed in detail in the article by Simona Cernea [7].

Another interesting avenue of treatment is the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Under normal conditions, the presence of SGLTs, which are located in the tubules of the kidney, ensure that no glucose appears in the urine. Glucose that appears in the renal tubules after glomerular filtration is reabsorbed by SGLT. SGLT-1 and SGLT-2 are the two well characterized transporter subtypes, which account for 100% glucose reabsorbed from the kidneys. Inhibitors of SGLT-2 that account for 90% of the effects are able to prevent glucose reabsorption in the kidney. The data from phase 3 trials on two drugs from the same family are now available. The article by Bhartia *et al*. reviews the current knowledge on this interesting drug development [8].

## Treatment of diabetes risk factors and complications - different target organs in T2D therapy

Extraglycemic effects of incretin hormones include weight control, positive effects on cardiovascular risk factors and beneficial renal and neuronal effects. Incretin mimetics are either weight neutral or they have a weight reducing effect. Together with their ability to prevent or delay the progression to impaired glucose states, incretin mimetics have been suggested for use in obese patients who have a high risk of developing diabetes. These aspects of incretin-based therapy are discussed in the article by Bagger and coworkers [9]. In addition to incretin therapy, obesity is currently treated by interventions in peptideric systems using neuropeptides or peripheral gut peptides like the PP-fold peptide YY, pancreatic polypeptide, amylin, and the gastric hormone ghrelin. This new line of research is presented in the article by Greenwood and coworkers [10].

As mentioned above, incretin-based therapy is also suggested to have beneficial CV effects. GLP-1 was found to reduce infarct size in animal models in the context of acute myocardial ischemia, which depends on the activation of pro-survival pathways including PI3-kinase, Akt, and ERK1/2. Ongoing research is currently investigating the relevance of these observations in human disease and underlying mechanisms, which is reviewed in the article by Michael Lehrke and Nikolaus Marx [11].

Excessive expansion of cardiac adiposity can lead to myocardial damage and cardiomyopathy. Accumulation of fatty acids (FA) and triglycerides can also impair glucose utilization and increase the production of reactive oxygen species and inflammatory molecules, which may finally lead to myocardial inflammation and dysfunction. In the review by Maria Guzzardi and Patricia Iozzo, evidence supporting a causal relationship between FA overload and cardiac dysfunction is examined [12]. The article also highlights the mechanisms of inflammation development in the fatty heart, and summarizes the available evidence in humans.

Besides incretin therapy there are several other pathways that have been tested to slow the progression to cardiovascular and renal failure. Preliminary studies on surrogate markers for renal outcome show great potential for additive renal protection. Beyond the use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), novel interventions in the renin-angiotensin-aldosterone-system with direct renin inhibitors or aldosterone antagonists have recently been found to have additive effects on ACEI and ARB. Other novel interventions include: endothelin-antagonism, suppression of inflammation with pentoxyfillin, MCP-1 synthesis inhibitors, or with Nrf2 agonists. All these novel therapy options are analyzed in the article by Hiddo Heerspink and Dick de Zeeuw [13].

GLP-1 also has an influence on the gut-brain and brain-periphery axes. GLP-1 can induce metabolic actions by interacting with its receptors expressed on nerve cells in the gut and the brain. It can also be considered as a neuropeptide synthesized by neuronal cells in the brain stem that release the peptide directly into the hypothalamus. In this environment, GLP-1 is assumed to

 

control numerous metabolic and cardiovascular functions such as insulin secretion, glucose production and utilization, and arterial blood flow. The article by Cendrine Cabou and Remy Burcelin highlight the latest data supporting the role of the gut-brain and brain-periphery axes in the control of glucose homeostasis [14]. Understanding the physiological role of GLP-1 will be helpful in the development of GLP-1-based therapies to control glycemia in type 2 diabetes by triggering the gut-brain axis or the brain directly.

Type 2 diabetic patients are characterized by exaggerated glucagon levels contributing significantly to hyperglycemia in these patients. Glucagon is the main secretory product of the pancreatic alpha-cells. It is therefore obvious to consider targeting the alpha-cell as potential therapy intervention in type 2 diabetes. In this regard and following preclinical evidence, drugs have been developed, which are able to suppress glucagon secretion and antagonize the glucagon receptor. In the review article by Mikkel Christensen *et al*., the physiological actions of glucagon and the role of glucagon in type 2 diabetic pathophysiology are outlined [15]. Furthermore, potential advantages and limitations of antagonizing the glucagon receptor or suppressing glucagon secretion in the treatment of type 2 diabetes are reviewed, with the focus on already marketed drugs and drugs in clinical development.

## Outcome lessons learned from large clinical trials

Several large clinical trials have been performed with different endpoints to assess treatment options in T2D. Generally, the risk for developing diabetic microvascular complications decreases when HBA1c is at target, while the effect on macrovascular complications is still unclear. Cristina Bianchi and Stefano Del Prato summarize the risks and benefits of tight glycemic control, as detailed in recently published large outcome studies [16]. They discuss the need for early intervention and personalized targets in relation to risks and benefits proposing HbA1c and ABCD of glycemia management in T2D. ABCD allows individualization of glycemic targets based on age (A), body weight (B), complications (C), and disease duration (D) to increase efficacy of glucose control for reducing micro- and macrovascular complication with minimal risk to the patient.

## Conclusions

Achieving the goal of glucose control in type 2 diabetes is still a great burden in most patients. Moreover, with conventional therapy, weight gain, hypoglycemia, and occasionally increased mortality are barriers to maximal therapy. Accordingly, micro- and macrovascular complications are still of great concern in these patients.

There is therefore a continuing need for drug development and clinical trials to assess the additive effect of new drugs on blood glucose control and diabetic complications. Incretin-based therapies as well as SGLT-2 inhibitors improve blood glucose control by unique mechanisms. They have advantages in that they tend to reduce weight and cardiovascular risk factors, and the risk of inducing hypoglycemia is low. They may also be cardioprotective, an issue that will be resolved when several outcome studies on both GLP-1 agonist and DPP4 inhibitors are completed.

Presently, we are aiming to set a target goal for HbA1c according to individual patients, considering their age, body weight, severe complications, and disease duration. Incretin-based therapy is becoming the preferred second-line therapy after metformin because of its positive effect on weight and cardiovascular risk factors and the relatively low risk of hypoglycemia. SGLT-2 inhibitors, if and when approved by the FDA and EMA, will be another important tool to control blood glucose control at any stage of therapy independent of insulin action. Since microvascular disease, mainly nephropathy, is still very common in uncontrolled type 2 diabetes, new therapies, other than ACEI or ARB, are needed to postpone end-stage organ disease in diabetes.

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