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
Continuing Need for Drug Development

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Indicates 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.

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 synergistic 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,

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
two compounds are available; firstly, exenatide (first approved agent by FDA in 2005) followed by liraglutide (approval in 2009). Sitagliptin, vil-
dagliltip, and saxagliptin are the DPP-4 inhibi-
tors, 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 step-
wise, additive manner when specific targets are
not reached. However, this approach does not pre-
vent 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 inter-
ventions, and finally, even in combination with in-
sulin. The benefits of incretin therapy at various
stages of diabetes are reviewed in detail in the ar-
ticle 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 character-
ized 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 in-
dude weight control, positive effects on cardiovas-
cular risk factors and beneficial renal and neu-
ronal effects. Incretin mimetics are either weight
neutral or they have a weight reducing effect. To-
gether with their ability to prevent or delay the
progression to impaired glucose states, incretin
mimetics have been suggested for use in obese pa-
tients who have a high risk of developing diabetes.
These aspects of incretin-based therapy are dis-
cussed in the article by Bagger and coworkers [9].
In addition to incretin therapy, obesity is cur-
tently treated by interventions in peptideric sys-
tems using neuropeptides or peripheral gut pep-
tides like the PP-fold peptide YY, pancreatic poly-
peptide, amylin, and the gastric hormone ghrelin.
This new line of research is presented in the arti-
cle 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 mod-
els 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

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 in-
flammatory molecules, which may finally lead to
myocardial inflammation and dysfunction. In the
review by Maria Guzzardi and Patricia Iozzo, evi-
dence 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 re-
nal outcome show great potential for additive re-
nal protection. Beyond the use of angiotensin con-
verting 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 inflamma-
tion with pentoxyfillin, MCP-1 synthesis inhibi-
tors, or with Nrf2 agonists. All these novel therapy
options are analyzed in the article by Hiddo Heer-
spink 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 syn-
thesized by neuronal cells in the brain stem that
release the peptide directly into the hypothala-
mus. 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 cardio-protective, 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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**References**