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# Medications for type 2 diabetes: how will we be treating patients in 50 years?

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## Abstract

The past 50 years have seen the development of many new options for treating and preventing type 2 diabetes. Despite this success, the individual and societal burden of the disease continues unabated. Thus, the next 50 years will be critical if we are going to quell the major non-communicable disease of our time. The knowledge we will gain in the next few years from clinical studies will inform treatment guidelines with regard to which agents to use in whom and whether more aggressive approaches can slow the development of hyperglycaemia in those at high risk. Beyond that, we anticipate identification of novel targets and techniques for therapeutic intervention. These advances will lead to more personalised approaches to treatment. Most importantly, we will need to focus our political and economic efforts on enhancing and implementing public health approaches aimed at prevention of diabetes and its co-morbidities. This is one of a series of commentaries under the banner ‘50 years forward’, giving personal opinions on future perspectives in diabetes, to celebrate the 50th anniversary of Diabetologia (1965–2015).

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## Introduction

The rise in the prevalence of obesity has contributed to the dramatic increase in the number of cases of type 2 diabetes being observed in all strata of society around the globe. The basis for this is a gene–environment interaction in which beta cell dysfunction, typically on the background of insulin resistance, is critical for the increase in glucose levels observed in impaired glucose metabolism and for the development of the hyperglycaemia of type 2 diabetes [1]. As reducing the extent of hyperglycaemia decreases the rate of development of microvascular complications and may benefit cardiovascular outcomes, ensuring adequate glucose control is essential. Preventing the disease would be better still. Over the past 50 years we have seen tremendous advances in therapy for type 2 diabetes; the next 50 years promise to be even more interesting and will hopefully have a greater impact on diabetes.

## History of approaches to the treatment of type 2 diabetes—from then to now

Following the first use of insulin as a therapeutic agent in 1922, there has been steady progress, with the introduction of eleven new classes of agents for treating hyperglycaemia in type 2 diabetes over the past half-century or so (Fig. 1). In addition, a number of modified insulins have been approved for the same purpose.

Over this period we have also witnessed the development of algorithms advising on how best to approach patients with hyperglycaemia. The EASD, in partnership with the ADA, currently recommend that metformin be the staple approach and the choice of second agents be individualised [2]. In addition, given the results of a host of studies examining approaches for diabetes prevention, both lifestyle and metformin are recommended in individuals at high risk of the disease, although the latter has not received formal approval from regulatory authorities. And with these approaches, one must not lose sight of treating co-existing conditions such as dyslipidaemia and hypertension.

Despite the giant strides forward over the last 50 years, it should not be forgotten that one size does not fit all. This is important, not only in terms of choices for the individual patient, but also when one considers healthcare systems around the world where many patients do not have access to all the different medications.

## Future prospects for the treatment of type 2 diabetes—looking forward 50 years

While we now have numerous classes of oral agents and injectables with variable effectiveness in lowering glucose, we have learned that they are not capable of preventing

progression of the beta cell lesion of type 2 diabetes [3]. In fact, the greater prevalence of severe insulin resistance linked to morbid obesity has prompted the development of more concentrated insulins that are now frequently required to maintain glucose control. We need novel therapies that are not only potent in terms of their capability of normalising glucose, but also have the ability to slow the progression of the disease. Furthermore, in an ideal world they would produce weight loss or, at worst, be weight neutral. For the remainder of this commentary we examine some of what we would expect to see in the next five decades as we strive to reduce the toll of type 2 diabetes.

## Ongoing clinical trials

There are currently a number of clinical trials at stages varying from recruitment to near completion. These have been designed in response to the need for better approaches to prevent diabetes, for the determination of best choices when considering second-line therapy following metformin, and to demonstrate cardiovascular safety.

In a little over the past decade, it has been clearly demonstrated that we can slow the development of type 2 diabetes in those at high risk. Major studies performed worldwide clearly demonstrate that it is possible to slow the development of frank diabetes, with lifestyle intervention reducing the risk by up to 58%. Metformin and the thiazolidinediones have been the most effective medications, with the latter arguably being more effective than lifestyle. What we have also learned is that normalising glucose for even a brief period while intervening to prevent diabetes will halve the rate of progression to diabetes relative to that if normoglycaemia is never achieved [4]. With this in mind, a consortium in the USA is undertaking the Restoring Insulin Secretion (RISE) study, examining the relative effectiveness of medications in adults (metformin alone, liraglutide plus metformin, and glargine followed by metformin, all vs placebo), medications in children (metformin alone, and glargine followed by metformin), and laparoscopic gastric band surgery vs metformin in adults [5]. The primary goal is to determine whether aggressive lowering of glucose levels can prevent the loss of beta cell function that characterises the transition from impaired glucose tolerance to diabetes. Importantly, participants in the medications studies will be treated for 12 months and studied at the end of active treatment and again after a 3 month medication washout period to determine whether improvements in beta cell function can be maintained when the active intervention is no longer in place. Should RISE find one or more interventions to be promising, it is likely that a larger clinical trial will follow.

As mentioned previously, the EASD and ADA have developed recommendations for treating patients with type 2 diabetes [2]; the choices recommended are based in part on studies performed by the pharmaceutical industry for registering their compounds. However, there are inadequate head-to-head comparisons of many of the different classes of compounds. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will directly compare one representative medication from four different classes: sulfonylureas (glimepiride), dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin), glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide) and basal insulins (glargine) in a long-term clinical trial in patients with diabetes for 10 years or less

[6]. One would hope that thorough evaluation of the comparative effectiveness over years of treatment with these medications will follow, to inform clinical decision-making.

Following the controversy regarding the potential increase in cardiovascular risk associated with thiazolidinedione therapy, regulatory authorities now require large studies to demonstrate the cardiovascular safety of newly developed glucose-lowering medications. These clinical trials require inclusion of many patients who are at high risk of, or have already had, a cardiovascular event. A few studies have already reported, with many more to come. Two trials of DPP-4 inhibitors, namely, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE), showed no increased risk of major adverse cardiovascular events [7, 8]. Since many had touted a potential cardiovascular benefit of compounds acting through the incretin system, the findings in this regard were somewhat disappointing. Additional safety assessments conducted as part of this programme identified an increased risk of hospitalisation for heart failure with saxagliptin; however, it is unclear whether this is a class effect or not. Further studies with other DPP-4 inhibitors will provide more information on these issues. One of these studies, the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), will also test whether linagliptin has a safer cardiovascular profile than the sulfonylurea glimepiride, providing further information related to the long-standing controversy regarding sulfonylurea safety, which was initially raised by the University Group Diabetes Program in the 1970s [9]. In addition to these studies, others examining the safety of GLP-1 receptor agonists, sodium–glucose co-transporter 2 (SGLT2) inhibitors and new long-acting insulins are on the horizon. While some have questioned the cost–benefit of these large safety studies, we earnestly request that the companies undertaking these trials make the data available for further analyses and subsequent publication, as they will provide rich data on both medication safety and efficacy, as well as the natural history of diabetes.

## New therapies—new targets and beyond

Our understanding of the pathogenesis of type 2 diabetes continues to drive the identification of novel and new therapeutic targets. These targets are located in the ‘traditional’ organs, comprised of the liver, fat, muscle and pancreatic islet, and more recently the ‘non-traditional’ targets, including the intestine, kidney, brain, macrophage and adrenal gland (Fig. 1). Those listed in the figure as possibilities for the period ‘2015–2065’ are those currently known by the authors as being pursued, but do not represent all possibilities. For example, as the understanding of the role of the brain in regulating metabolism broadens, it is likely that a number of central targets will emerge. Importantly, we must develop interventions to stop or reverse the loss of beta cell function and mass. Thiazolidinediones have, to date, been the most effective approach [3], most likely because they reduce ‘afterload’ on the beta cell and thereby decrease secretory demand and slow disease progression. That said, new approaches are needed. Some novel targets may be identified from studies addressing the mechanisms of the improved glycaemic control that is frequently observed before the occurrence of significant weight loss following bariatric

surgery—a treatment approach that was not seriously considered for type 2 diabetes just a few years ago.

Aside from new targets, work continues on additional approaches with existing molecules. One aim is to produce an insulin with reduced risk of hypoglycaemia by decreasing variability in absorption and action and creating hepatoselective formulations that mimic portal insulin activity. More aspirational efforts aim to construct insulin formulations that are glucose responsive, with enhanced activity at high glucose and essential but lower activity at normal glucose. A different engineering challenge is to modify peptides such as GLP-1 and insulin for oral delivery. Automated mechanical devices delivering both insulin and glucagon to 'replace' the islet are near at hand, but require much refinement to be reasonable approaches for type 2 diabetes care [10].

Another expected change in treatment approaches will be a broader use of combination therapies. We have already observed this in terms of oral agents that typically combine a newer agent with an older one, the latter frequently metformin. Future oral combination medications will also probably include two new agents, with one of the first such combinations being DPP-4 and SGLT2 inhibitors. We will certainly see triple oral glucose-lowering medications and a 'polypill' that is not solely aimed at lowering glucose. Finally, combination therapy will include injectable agents. Development of these has already reached the marketplace in combinations of a basal insulin and GLP-1 receptor agonist [11]. Animal studies involving new monomeric peptides that have agonistic properties at more than a single site have been shown to reduce body weight and improve glycaemia by combining activity at GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors [12].

## Pragmatic clinical trials

The common approach to testing the effectiveness of medications is the randomised clinical trial. In the future, greater use of pragmatic clinical trials for assessing the therapeutic value and adverse effect profiles of medications will be employed to enhance the speed and reduce the cost of the increasing numbers of trials needed. Such studies require large numbers of patients who are broadly representative and therefore could also evaluate effects in patient subgroups. Comparative effectiveness research exploring available datasets to elucidate treatment responses in populations are emerging today. The future also promises randomised comparisons as part of routine care [13].

## Personalised medicine—hope created in part by genetics

A development that seems certain in the next 50 years is a greater focus on personalised medicine. Clearly, with their hyperglycaemia management guidance [2], the EASD and ADA have pointed us in that direction. That said, the rapid advances in genetics, epigenetics and metabolomics will surely provide additional targets and tailoring opportunities for therapeutic intervention. We should be able to examine an individual's genetic material and, together with their metabolic phenotype, be able to select and monitor optimal agent(s) for achieving and maintaining health for extended periods. As we further understand the complexities, RNA- and DNA-based therapeutics will certainly emerge.

## Stem cell therapy—a pipe dream?

While the focus of this commentary has been on what to expect in terms of medications, one cannot ignore the potential of beta cell replacement therapy. This concept has been the ideal for many years, but with the limited number of viable islets and the need for immunosuppression, it has been limited to a very few, and the outcomes have not always been favourable. An early phase study recently commenced using embryonic stem cell-derived cells as replacement therapy in type 1 diabetes (ClinicalTrials.gov identifier: NCT02239354). Furthermore, the push continues for approaches to convert human pluripotent stem cells into beta cells, and a recent report suggested that we may be getting closer [14]. However, it must be remembered that such fanfare has greeted many previous reports and these have not materialised into game changers. But, with a 50 year timeline, it is hard to imagine that the technical hurdles will not be overcome to produce beta cells of sufficient quantity and quality, as well as protecting them from the primary disease process.

## Concluding remarks

One could argue that we have the technology today to allow people with diabetes or those at risk to live normal lifespans free of disabling complications. Certainly, there has been a massive failure on a global scale to consistently implement healthy living recommendations, provide sufficient patient education/ empowerment, monitor disease progression and prescribe adequate pharmaceutical intervention. A large determinant of that failure relates to politics and economics, which we must recognise as critical factors. Advances in public health sciences and implementation research will be required to blunt the tremendous and increasing toll that type 2 diabetes inflicts on individuals and societies [15]. It is up to us to ensure that over the next 50 years the expected tremendous advances in our approaches to treating and, more importantly, preventing diabetes have the maximum possible impact.

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## Abbreviations

| | |
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| **DPP-4** | Dipeptidyl peptidase-4 |
| **GLP-1** | Glucagon-like peptide-1 |
| **RISE** | Restoring Insulin Secretion |
| **SGLT2** | Sodium–glucose co-transporter 2 |

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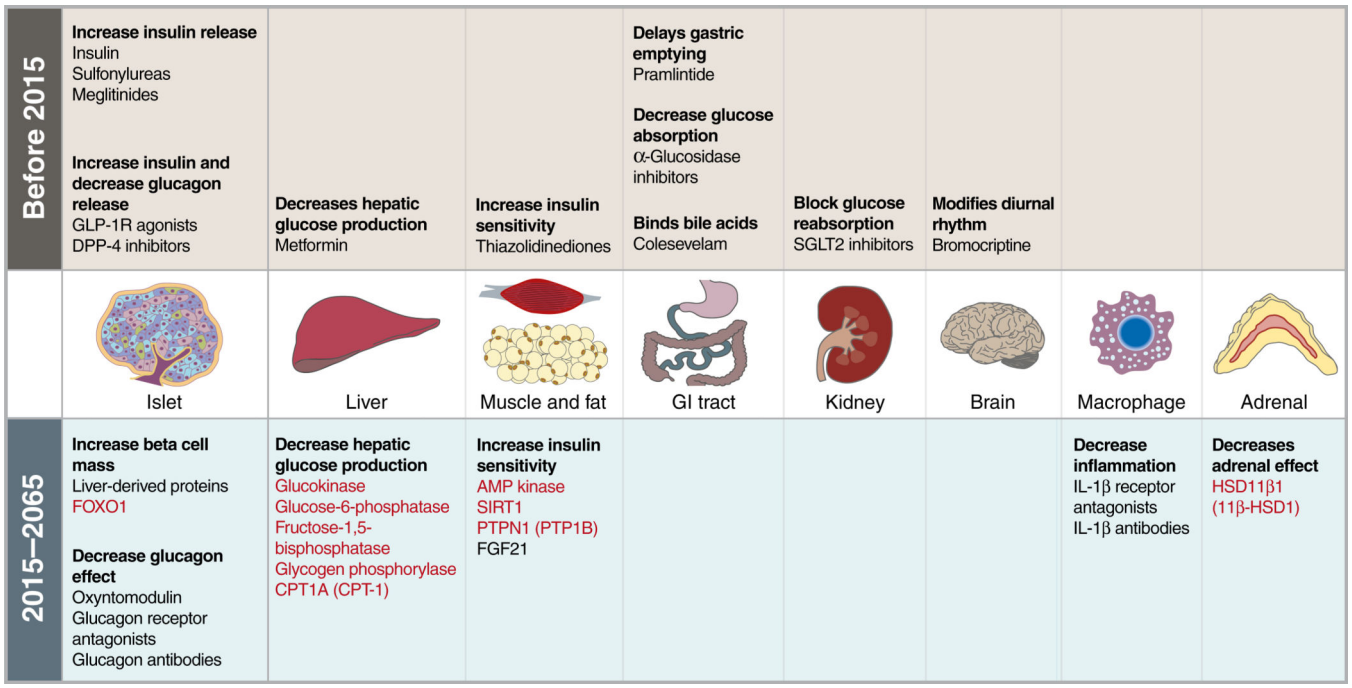


**Fig. 1.**

Currently available glucose-lowering medications and future targets subdivided by the organ system in which they have their primary effect. Medications with their general mode of action that were developed before 2015 are listed above the organs, while currently identified future medications (black text) and targets (red text) with their general mode of action are listed below the organs. It is anticipated that over the next 50 years many more targets will be identified. CPT1A, carnitine palmitoyltransferase 1A; FGF21, fibroblast growth factor 21; FOXO1, forkhead box protein O1; GI, gastrointestinal; HSD11β1, 11β-hydroxysteroid dehydrogenase type 1; SIRT1, sirtuin 1; PTPN1, protein tyrosine phosphatase, non-receptor type 1