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Viewpoint

Exciting breakthroughs in the management of diabetes mellitus

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ABSTRACT

Remarkable advances were observed in recent years in the management of patients with type 2 (T2DM) or type 1 (T1DM) diabetes mellitus. Regarding T2DM, changes in treatment paradigms were observed, moving from a glucocentric approach to a multi-risk strategy and, finally, in people at high risk, to a specific cardiorenal protection using new antidiabetic agents. Regarding T1DM, progresses combined new insulin analogues with better pharmacokinetics, continuous and flash glucose monitoring and improved insulin delivery systems with smart insulin pens and insulin pumps connected to glucose monitoring device, allowing better glucose control with less hypoglycaemia. Because of an increasing variety of therapeutic approaches, an individualized patient-centred strategy is recommended, ideally with the collaboration of a multidisciplinary team. Shared care, connected care and tele-medicine will play an increasing role in the management of T1DM, and most probably also T2DM, in a near future.

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Introduction

Following an already long history of better understanding and care [1], the management of diabetes has made huge progress during the last decade, both for type 2 (T2DM) and type 1 (TIDM) diabetes mellitus. Indeed, many pharmacological [2] and technological [3] advances have positively affected and continue to shape diabetes management, with new promising prospects in a near future (Fig. 1).

Management of T2DM

T2DM is a more complex disease than initially expected and its management should target multiple defects that contribute to hyperglycaemia. Choices for the treatment of T2DM have multiplied [4] as our understanding of the underlying pathophysiological defects has evolved. The complex interplay of insulin secretion and insulin resistance developed from previously known “triumvirate" to "ominous octet" underlines the implication of multiple organs in glucose metabolism [5]. The more recent demonstration of a so-called incretin defect in the gut, on the one hand, and increased tubular glucose reabsorption in the kidneys, on the other hand, paved the route for the development of new therapies: respectively, incretin-based medications, both dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists [6], and sodium-glucose cotransporter type 2 (SGLT2) inhibitors [7]. Of note, these medications are associated with a low risk of hypoglycaemia and some weight loss, which contrast with what is commonly observed with classical antidiabetic agents as sulphonylureas and insulin. The intriguing contribution of the microbiome in the pathophysiology of T2DM and cardiovascular disease also opens the window for new therapeutic approaches, which, however, require further validation [8].

An important feature of T2DM is that the disease is commonly associated with other cardiovascular risk factors such as abdominal obesity, arterial hypertension, atherogenic dyslipidaemia and prothrombotic state. As a consequence, management of T2DM should follow a patient-centred approach that considers, beyond glycaemic control, all risk factors together [9, 10]. As a consequence, in addition to background life-style measurements, polypharmacy is commonly required to achieve targets in patients with T2DM and most people are taking antihypertensive agents, statins and antiplatelet compounds in addition to their glucose-lowering medications. Of major interest, this multi-risk therapeutic strategy (instead of a pure glucocentric approach) proved its efficiency to improve overall prognosis of patients with T2DM [11]. Especially, it allows a remarkable progressive reduction in major cardiovascular events and cardiovascular death during the last two decades [9], even if the residual risk remains higher in patients with T2DM compared to non-diabetic individuals [12].

As a complement to a standard care approach, new classes of diabetes drugs have emerged that can improve cardiovascular prognosis

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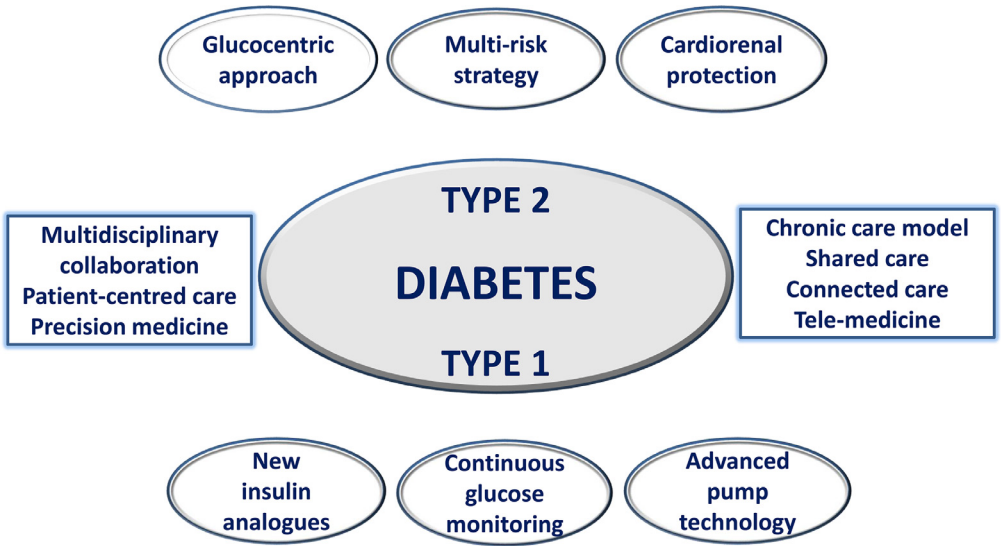

Fig. 1. Advances in the management of both type 1 and type 2 diabetes.

in patients with T2DM at high cardiovascular risk [2, 10]. Both GLP-1 receptor agonists [13] and SGLT2 inhibitors [7] reduce cardiovascular outcomes and mortality [14]. SGLT2 inhibitors also showed a consistent and remarkable reduction in hospitalisation for heart failure and slowed renal function decline, including the progression to end-stage renal disease and renal death [2, 7]. Interestingly enough, the positive effects reported with SGLT2 inhibitors occur largely independently of the improvement of blood glucose control [7]. This surprising observation for compounds that were initially developed as glucose-lowering agents contributes to profoundly change the treatment paradigm for the diabetic (but also non-diabetic) patients at high risk of cardiovascular (including heart failure) or renal disease [2, 9, 10]. Guidelines from cardiology societies even propose to use such new medications that have proven cardiovascular protection in place of metformin as first line-line therapy, yet this proposal remains a matter of controversy [15, 16]. What so ever, these new medications meaningfully increase the anti-diabetes armamentarium that should help patients with T2DM to live longer, with fewer severe complications and a better quality of life [17].

As obesity plays a major role in the pathophysiology of T2DM, drugs that more specifically target weight excess may be used, yet the past history of anti-obesity medications was strewn with pitfalls. In recent years, pharmacological approaches using peptides appeared promising [18]. GLP-1 receptor agonists are already currently used (possibly in combination with SGLT2 inhibitors) and GLP-1-GIP [glucose-dependent insulin releasing polypeptide] dual agonists are coming soon. Bariatric surgery is largely used in obese patients with severe and extreme obesity. The so-called metabolic surgery has gained much interest in the last decade for the management of some patients with T2DM and only moderate obesity, but resistant to medical interventions [19]. The benefit/risk balance of such intervention in these patients remains to be better evaluated.

Thus, the availability of new drug and non-drug therapeutic options for T2DM management enables individualized patient care with consideration of disease state, comorbidities, medication efficacy and safety profile, patient preference and cost. Personalized medicine aims at better targeting therapeutic intervention to the individual to maximize benefit and minimize harm. The contribution of pharmacogenetics and pharmacogenomics to personalized therapy is rapidly progressing but still needs to mature greatly before routine clinical implementation would be possible [20].

Management of T1DM

The management of T1DM still relies on the subcutaneous administration of insulin, a century after its discovery [1, 21]. The more recent advances regarding insulin preparations are the launch of basal and ultra-rapid analogues of human insulin with improved pharmacokinetics. Overall, their combinations in so-called basal-bolus regimens contribute to more accurately mimic the profile of endogenous insulin secretion both in the fasting and postprandial states. These new insulin analogues allow a more stable and reproducible glucose equilibrium at night and a better control of postprandial hyperglycaemia, together with a reduced risk of hypoglycaemia [22]. Nevertheless, obtaining an optimal glucose control remains a challenge for many patients with T1DM. Further advances may result from the development of “intelligent” insulin preparations (i.e. polymer-based and intrinsic glucose-responsive insulin analogues), which promise to enhance the safety and efficacy of insulin replacement therapy [23].

Besides pharmacotherapy, technological innovations play an important role in diabetes management [3], especially for patients with T1DM [24]. Insulin administration without concomitant regular home blood glucose monitoring (HBGM) cannot be successful. For a long time, HBGM was made using finger-sticks and a glucose metre, with many constraints and limitations, even it was already a huge progress compared to glucosuria measurements. Evolving technology has led to the development of innovative glucose-sensing methods. Continuous glucose monitoring (CGM) and flash monitoring technology now offer systems to record glucose readings throughout the day and detect trends in glucose levels. These systems allow to analyse the glucose variability, an underestimated parameter, and to implement new glucose metrics (“time in range”, “time above range” and “time below range”), which may provide additional valuable information to both patient and health-care providers, in complement of the measurement of glycated haemoglobin [25]. These new approaches of HBGM contribute to increase patient's quality of life while improving both the efficacy and safety of insulin therapy [3].

Evolving technology has led also to the development of innovative insulin delivery systems. The use of smart insulin pens (with an associated electronic device enabling connectivity, or with a memory function) holds promise for improving and simplifying diabetes self-management [26, 27]. Insulin pump technologies are advancing at an extraordinary rate and have potential to further improve diabetes

outcomes [3]: successively, sensor-augmented pumps (i.e. insulin pumps that pair to a CGM system, displaying CGM sensor glucose data on the pump's home screen and thus allowing diabetic users easy access to the glucose monitoring information), insulin pumps with hypoglycaemia suspension (i.e. suspension of insulin delivery in response to hypoglycaemia or anticipated hypoglycaemia, based on CGM data), and pumps with automated insulin delivery (i.e. hybrid closed-loop system, which dynamically modulates basal insulin delivery but still requires users to deliver bolus doses for meals using an algorithm and a bolus calculator, an intermediate step towards "artificial pancreas") [28]. Such new features enable better glycaemic control and prevent both severe hypoglycaemic and hyperglycaemic episodes, thereby mitigating the risk for acute and chronic complications [3]. In the future, tools to support decision making may help patients and health-care providers to use the output of these devices to optimise diabetes management [24].

Plea for an integrated multidisciplinary and patient-centred management

Because of recent advances in the management of both T1D and T2D, an integrated multidisciplinary approach is increasingly recommended (Fig. 1).

For patients with T2D, a better collaboration between first-line health care providers (general practitioners, nurses, dietitians), and specialists (endocrinologists), is mandatory and networks should be implemented to improve such a cooperation. Furthermore, diabetes care should be aligned with components of the "chronic care model" to ensure productive interactions between a prepared proactive practice team and an informed activated patient. This model emphasizes patient-centred team care, integrated long-term treatment approaches to both diabetes and comorbidities, and ongoing collaborative communication between all team members [29]. Finally, because of the recent findings of a cardiovascular and renal protection with GLP-1 receptor agonists and SGLT2 inhibitors, a more efficient integrated care between endocrinologists, cardiologists and nephrologists is also increasingly recommended.

Technological innovations opened the route to the so-called connected care helping to shape new approaches to diabetes care with the help of a multidisciplinary team, including diabetes educators. It is important for all members of this team to keep up with the latest therapies and technologies for optimal clinical care of people with T1DM. New technologies allow for individualisation of care, as diabetic patients are able to work with their health-care providers (shared care) to determine which systems best fit their lifestyle and needs [3]. Tele-medicine and connected care will most probably and progressively replace more restrictive and expensive face-to-face clinic visits. Such new models of care increase velocity-to-control with more frequent and pertinent interventions that speed the achievement of glycaemic goals. While modern technology is now successfully adopted by an increasing number of patients with T1DM, there is emerging evidence to support its use to also improve the management of people with T2DM. However, further research is required to demonstrate the long-term clinical benefit and financial viability of this costly technology in this large population of patients with T2DM [30].

Finally, the COVID-19 pandemic has added an enormous toll to the existing challenge of diabetes care [31]. The current clinical management of diabetes requires a shift in patient-provider interaction beyond the walls of clinics and hospitals, with an increasing used of tele-medicine when feasible [32].

Conclusion

Successful integration of innovative pharmacological therapies, more efficient glucose monitoring systems, and revolutionary-enabling technologies applied to healthcare represent an historical opportunity to improve diabetes management and thereby the quality of life of people with diabetes. Because the treatment spectrum for the management of both T1DM and T2DM has rapidly advanced in recent years and most probably will continue to do so in the coming years, it seems important to propose to the medical community a journal that more specifically focuses on diabetes management. This is the objective of the new open access journal "Diabetes Epidemiology & Management".

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