Present and future challenges in Type 2 diabetes

According to the International Diabetes Federation, more than 285 million people (6.4% of the world population) are currently estimated to suffer from diabetes, a figure which is expected to rise to 438 million (7.8%) by 2030. Moreover, the World Health Organisation calculates that nearly three million deaths worldwide are attributable to diabetes each year; by 2030, this figure is expected to double. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of the cases of diabetes. These astonishing statistics help to illustrate the epidemic prevalence of T2DM, and the major need for effective diagnostic, intervention and disease management strategies.

By Dr Lesley J Millatt, Dr Rémy Hanf and Dr Dean W Hum

Prediabetes is presently defined as moderately elevated fasting blood glucose (FBG), and is estimated to affect 79 million adult Americans, or 35% of the adult population. This altered glucose metabolism state is associated with an increased risk of developing T2DM (**Figure 1**), although other parameters including excess adiposity, inflammation and dyslipidemia are risk factors associated with the development of insulin resistance, loss of pancreatic function, worsening of hyperglycemia and progression to diabetes[1].

Type 2 diabetics, but also prediabetics, are at increased risk for a wide range of debilitating diseases and diabetes is the leading cause of new cases of kidney failure and blindness and of non-traumatic lower limb amputation. Moreover, cardiovascular disease (CVD) is 2-4 times higher in diabetics[2]. An emerging lesser known, but potentially fatal complication of T2DM is the accumulation of fat in hepatocytes (steatosis), that leads to the chronic liver disorder Non-Alcoholic Fatty Liver Disease (NAFLD) and its more advanced form, Non-Alcoholic Steato-Hepatitis (NASH). NAFLD/NASH can progress to hepatitis, cirrhosis, and even liver cancer, thus illustrating the importance of addressing these serious complications of T2DM.

Despite beneficial effects of current glucose-lowering treatments, disease-related morbidity and mortality remain considerable in T2DM patients, galvanising the search for innovative medications that target the multiple metabolic abnormalities as well as inflammatory processes and other pathways predisposing to diabetes-associated disorders. One of the greatest challenges in T2DM disease management is the prevention of its long-term complications and the treatment of associated disorders, including NAFLD/NASH and CVD.

Prospective studies in T2DM have shown an association between the degree of hyperglycemia

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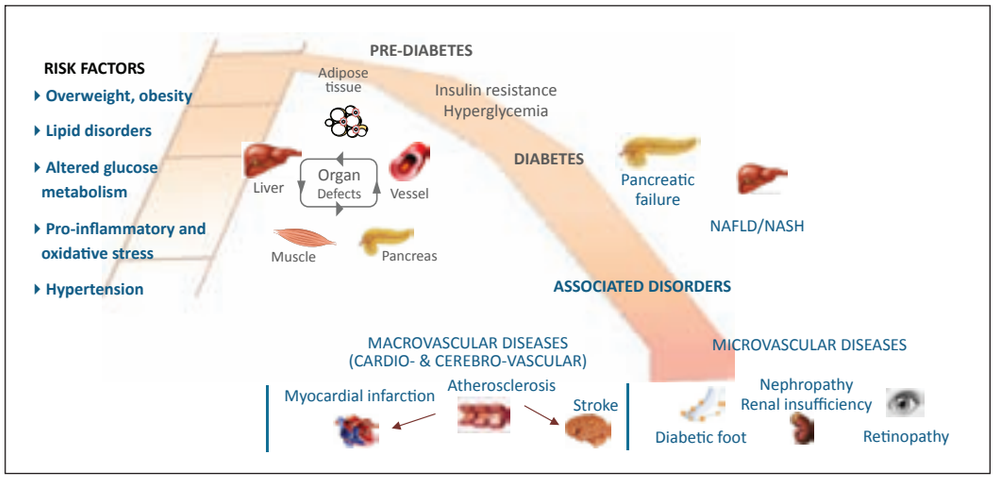

Figure 1: The pathophysiology of pre-diabetes and diabetes. T2DM may be visualised as an evolving pathophysiological process in which multiple risk factors accumulate to induce the pre-diabetic state of insulin resistance and moderate fasting hyperglycemia. The decreased insulin sensitivity of organs such as the liver, skeletal muscle and adipose tissue results in increased glucose output and reduced glucose uptake, leading to compensatory insulin over-secretion from the pancreas. The progressive development of pancreatic beta cell dysfunction and loss of beta cell mass ultimately lead to impaired insulin secretion and a chronic hyperglycemic state, the definition of overt T2DM. Chronic hyperglycemia and inflammation contribute to the development of associated micro- and macro-vascular disorders, including the liver disorders Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steato-Hepatitis (NASH)

and the risk of micro- and macrovascular complications, including fatal CVD events. However, the recent ACCORD and ADVANCE trials in patients with longstanding T2DM have shown that aggressive glucose control in such patients has no clear benefits, or may even increase CVD events[3]. Therefore, other independent risk factors may exist that contribute significantly to CVD risk in these patients. Alternatively, such findings may simply reflect the limitations of current anti-diabetic therapies, due to off-target effects that counter the potential benefits of glucose lowering.

New therapeutics must therefore address the multi-factorial nature of T2DM, and aim to treat diabetic patients at an earlier stage of the disease, if pharmacological interventions hope to halt the epidemic.

Current and future therapeutic approaches

Current widespread treatments for T2DM include metformin (suppressor of hepatic glucose production), sulfonylureas (insulin secretagogues), and the thiazolidinedione pioglitazone (PPAR agonist). More recent incretin-based treatment strategies include glucagon-like peptide-1 (GLP-1) mimetics and inhibitors of the enzyme that degrades GLP-1, dipeptidyl peptidase-4 (DPP-4). GLP-1 is an intestinally-derived peptide that stimulates insulin secretion in response to food intake, as well as reducing the rate of gastric emptying, thus promoting satiety and weight loss. Despite a certain number of gastrointestinal side-effects, the GLP-1 mimetic exenatide was approved by the FDA in 2005, and its indication was extended in 2009 to standalone therapy for T2DM. A retrospective analysis of almost 40,000 patients treated with exenatide showed a reduced incidence of cardiovascular events[4], although these results should be confirmed by prospective studies.

New therapeutic approaches in the T2DM drug discovery pipeline are specifically designed to take into account the multi-factorial nature of T2DM by targeting multiple diabetes-related indications, and not simply focusing on glucose-lowering. Moreover, due to the elevated CVD risk in T2DM patients, current FDA recommendations require that all new anti-diabetic drugs show exemplary cardiovascular safety profiles. Thus, drugs that target molecular pathways potentially implicated in both diabetes and CVD are especially desirable. Such approaches include the targeting of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), GPR119, TGR5, sirtuin 1 (SIRT1), the sodium-glucose co-transporter 2 (SGLT2), and GPR40, for each of which the rationale is briefly described below (**Table 1**).

11β-HSD1: This enzyme mediates the generation of the glucocorticoid cortisol from its inactive precursor

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cortisone. Since cortisol increases insulin resistance, gluconeogenesis and glycogenolysis, the development of inhibitors for 11β-HSD1 provides a potential therapeutic anti-diabetic approach. Indeed, the treatment of murine T2DM models with such an inhibitor improved insulin sensitivity, hyperglycemia and other glycemic parameters[5]. Moreover, this same study showed that 11β-HSD1 inhibition was associated with decreased weight gain in a mouse obesity model, as well as a decrease in lipid parameters and lesion size in a murine atherosclerosis model. The oral, selective 11β-HSD1 inhibitor INCB13739, was tested in a Phase II clinical trial as a 12-week add-on therapy to metformin, and resulted in significant reductions in glycemic parameters, plasma lipid levels, and body weight[6]. However, a recently-published study with another 11β-HSD1 inhibitor, MK-0916, reported only modest beneficial effects of a 12-week treatment in patients with T2DM and metabolic syndrome[7]. Thus, further clinical studies are required to clarify the therapeutic interest of 11β-HSD1 inhibitors to address multiple aspects of the metabolic syndrome and, in particular, T2DM.

GPR119: This G protein-coupled receptor (GPCR) is predominantly expressed in pancreatic β-cells and in the gastrointestinal tract. GPR119 activation increases cAMP signalling, resulting in enhanced glucose-dependent insulin secretion and increased levels of GLP-1 and the related incretin GIP (Glucose-dependent Insulinotropic Peptide). Oral administration of small molecule GPR119 agonists has been shown to improve glucose tolerance in rodents[8], while molecules such as APD597[9] and MBX-2982 are in clinical development. Similar to GLP-1 mimetics, GPR119 agonists are also expected to have beneficial effects on obesity, and were indeed shown to decrease feeding, body weight gain, and adiposity in rats[10]. Thus, GPR119 represents an attractive potential target for both T2DM and associated obesity, although its cardiovascular effects remain to be determined.

TGR5: This widely expressed bile acid-activated GPCR has recently emerged as an attractive therapeutic target in T2DM, obesity, NASH and the metabolic syndrome in general. Similar to GPR119, TGR5 activation in the intestine results in cAMP accumulation and enhanced GLP-1 secretion[11]. In addition, TGR5 activation in the skeletal muscle enhances energy expenditure via increased thyroid hormone activity, and may have beneficial effects on obesity and insulin resistance[12]. Finally, TGR5 activation in liver macrophages has anti-inflammatory effects[13] and also enhances hepatic nitric oxide production[14], with potential beneficial effects on bile acid homeostasis and diabetes-associated liver injury. Evidence of the therapeutic potential of TGR5 in T2DM and associated pathologies was provided by a report of the beneficial effects of the specific TGR5 agonist INT-777 on body weight, hepatic steatosis, preservation of liver and pancreatic function, and maintenance of glucose homeostasis and insulin sensitivity in mouse models[15].

Table 1: Emerging therapeutic approaches to the global management of Type 2 diabetes

Drug target	Examples in development	Development phase	Mechanism of action	Anti-diabetic therapeutic benefits	Potential CV benefits
11β-HSD1	INCB13739 MK-0916	Phase II Phase II	Inhibition of generation of cortisol from cortisone	↓ insulin resistance ↓ glycemia	↓ weight gain ↓ lipids ↓ atherosclerosis
GPR119	APD597 MBX-2982	Phase I Phase II	↑ insulin secretion ↑ incretins	Improved glucose tolerance	↓ weight gain
TGR5	INT-777	Regulatory pre-clinical	↑ GLP-1 secretion ↑ thyroid hormone activity	Improved glucose homeostasis and pancreatic function	↓ weight gain Liver function preservation
SIRT1	SRT2104	Phase II	Activation of the NAD^+-dependent deacetylase SIRT1 that regulates metabolism and life-span	↓ insulin resistance ↓ glycemia	↓ atherosclerosis ↓ I/R injury ↓ neointima
SGLT2	Dapagliflozin BI-10773 LX4211	Phase III Phase III Phase II	↓ renal glucose reabsorption	↑ glucosuria Improved glucose homeostasis	↓ blood pressure Stroke protection
GPR40	Unknown	Pre-clinical ?	FFA-induced incretin secretion	Improved glucose tolerance (agonist) Improved insulin tolerance (antagonist)	Unknown
PPARα/δ	GFT505	Phase II	Specific PPAR agonism to address multiple cardiometabolic risk factors	↑ insulin sensitivity Improved glucose homeostasis	↓ dyslipidemia ↓ inflammation ↓ liver dysfunction

SIRT1: This NAD+-dependent deacetylase has been identified as one of the principal downstream mediators of the beneficial effects of caloric restriction on lifespan and metabolic parameters. Potent small molecule activators of SIRT1 have recently been identified, and were shown to improve insulin sensitivity, lower plasma glucose and increase mitochondrial capacity in murine obesity models, and to improve whole-body glucose homeostasis and insulin sensitivity in the Zucker rat T2DM model[16]. In addition to their beneficial effects on diabetes parameters, SIRT1 activators are expected to have pleiotropic cardioprotective effects. For example, SIRT1 over-expression has shown protection against atherosclerosis in a murine model, likely via anti-apoptotic effects in endothelial cells[17]. Furthermore, recent studies have demonstrated protective effects of SIRT1 over-expression on ischemia/reperfusion (I/R) injury in the heart[18], and on neointima formation following vascular injury in mice[19]. It will therefore be of great interest to determine the effect of SIRT1 activators on cardiovascular risk in clinical studies.

SGLT2: Via the transporter SGLT2, the kidney plays a key role in the regulation of glucose homeostasis, by mediating glucose reabsorption into the plasma. The development of SGLT2 inhibitors therefore holds promise for glycemic control in T2DM, since the inhibition of renal glucose reabsorption results in increased glucose excretion in the urine. A number of SGLT2 inhibitors (including dapagliflozin, BI-10773, and LX4211) have been developed, and are in the advanced stages of Phase II/III clinical trials, where they have shown efficacy on glycated haemoglobin (HbA1c) levels, fasting plasma glucose, glucose tolerance, weight loss and blood pressure lowering[20,21]. Moreover, SGLT inhibition may show additional cardioprotective effects, since a recent study showed that treatment with a SGLT inhibitor led to a reduction in infarct size and edema in a murine stroke model[22]. Thus, the results of Phase III clinical trials of SGLT2 inhibitors are awaited to determine their effects on CVD.

GPR40: Similar to GPR119, this free fatty acid (FFA)-activated GPCR is expressed in both pancreatic β-cells and in the endocrine cells of the gastrointestinal tract, where it mediates FFA-induced incretin secretion[23]. GPR40 over-expression in pancreatic β-cells has been shown to increase glucose-stimulated insulin secretion and improve glucose tolerance in normal and diabetic mice[24], and small-molecule GPR40 agonists improved glucose tolerance in mice with high-fat diet-induced obesity[25]. However, a recent study showed that the treatment of Zucker diabetic rats with a small-molecule GPR40 antagonist improved insulin tolerance, while having no effect on glucose tolerance[26]. Thus, the specific role of GPR40 in T2DM remains open to debate, and should be thoroughly addressed before proceeding with the clinical development of GPR40 modulators.

PPAR agonists

In addition to the new generation of potential anti-diabetic drug targets described above, opinion is evolving concerning the targeting of members of the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptor transcription factors.

The PPARγ agonist pioglitazone has shown beneficial effects on several clinical outcomes in prediabetic and diabetic patients, including reducing the overall risk of cardiovascular events (ProActive Study[27]), renal complications[28], and NASH/NAFLD[29]. Moreover, Roche is developing aleglitazar, a balanced mixed PPARα/γ agonist, for secondary cardiovascular prevention after myocardial infarction, with the promise of greater preventive effects due to reduction of multiple risk factors, as compared to current glitazone medications[30]. A Phase III clinical trial with aleglitazar is currently ongoing in patients with T2DM who have recently experienced a cardiac event. Interestingly, the primary endpoint of this study is not glycemic control, but cardiovascular events. Thus, future progress is likely to be focused on the development of PPAR agonists with specific profiles that enable them to address not only T2DM, but also its associated pathologies.

An emerging target in T2DM management is PPARδ, due to the positive effects of this PPAR sub-type on multiple features of the metabolic syndrome. Indeed, in pre-clinical studies, PPAR activation increased lipid catabolism in multiple tissues and improved the serum lipid profile, glucose homeostasis, and insulin sensitivity, while reducing inflammation and weight gain[31]. Finally, the FIELD[32] and ACCORD[33] studies showed that the PPARα agonist fenofibrate could lower the risk of retinopathy and diabetic nephropathy, as well as reducing CVD events in dyslipidemic patients, thus illustrating the interest of developing mixed PPARα/γ or mixed PPARα/δ agonists.

GFT505, a potent agonist of the PPARα and PPARδ receptors, shows a unique therapeutic

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profile, notably due to its activity on PPARδ. It thus targets multiple micro- and macrovascular risk factors including hyperglycemia and insulin resistance, atherogenic dyslipidemia, the proinflammatory state, and liver dysfunction. GFT505 is currently being developed for T2DM (HbA1c reduction), with a potential to address NAFLD/NASH, cardiovascular prevention in diabetics, and the microvascular complications of diabetes.

GFT505 has undergone Phase IIa clinical trials in pre-diabetic patients and in patients with atherogenic dyslipidemia (high triglycerides, low HDL-cholesterol)[34]. The data from pre-diabetic patients demonstrate that GFT505 treatment for 28 days results in a significant decrease in fasting plasma glucose, fasting plasma insulin and improvement of the insulin resistance index (HOMA). Furthermore, patients showed a significant reduction in LDL-cholesterol, in parallel with a reduction in triglycerides and an increase in HDL-cholesterol. Importantly, a study conducted in healthy volunteers demonstrated that GFT505 significantly lowered the fasting free fatty acid (FFA) plasma concentration, and potentiated the effect of a meal test on plasma FFA, which is indicative of increased insulin sensitivity[35].

GFT505 also shows significant beneficial effects on various abnormalities associated with NAFLD/NASH. Notably, GFT505 treatment reduced liver enzymes (alanine aminotransferase ALAT, gamma-glutamyltransferase γGT), and had anti-inflammatory effects[34]. Moreover, all trials have confirmed the excellent tolerability of GFT505, and the absence of PPARγ-related side-effects[34,35]. GFT505 is currently in advanced Phase II clinical trials.

Taken together, these clinical results provide compelling arguments for PPARδ agonists as a potential treatment for T2DM and associated disorders. Moreover, the beneficial effect of the PPARα/δ agonist GFT505 on liver enzymes in Phase IIa indicates that PPARδ agonism may show a unique potential for the treatment of NAFLD/NASH, for which no approved treatment exists.

A novel approach to new target identification

Beyond the present potential T2DM therapeutic targets being addressed, there is a need to identify other innovative non-glucosecentric approaches. Access to appropriate patient cohorts and clinical samples is important for novel target identification studies. A public/private research consortium (IT-Diab) has recently been established that focuses on recruiting rare patient cohorts for the purpose of identifying and validating new therapeutic targets in T2DM. One such cohort involves the recruitment of 500 pre-diabetic patients who will be followed longitudinally for up to five years, or until the onset of T2DM. Blood and tissue samples collected from these patients at regular time-points, followed by transcriptomics and proteomics studies, will provide valuable insight into the mechanisms and players involved in the progression from prediabetes to diabetes.

Another potential source of samples for the identification of novel targets is patients undergoing bariatric surgery, a common therapeutic solution to morbid obesity. Interestingly, a meta-analysis of 136 studies involving patients undergoing bariatric surgery showed that T2DM was completely resolved (defined as the ability to discontinue all diabetes-related medicines and to maintain blood glucose at normal levels) in an impressive 77% of affected patients[36].

The mechanism of diabetes resolution after bariatric surgery remains unclear, but is apparently independent of weight loss, since diabetes remission generally occurs in the days and weeks following surgery, prior to significant weight loss. It is believed that surgical manipulation of the gastrointestinal tract plays a direct role in T2DM regression due to effects on metabolic pathways resulting in enhanced insulin sensitivity and/or improved β-cell function. Two major hypotheses have been proposed to explain the dramatic effects of bariatric surgery on glycemic control. The 'lower intestinal hypothesis'[37] suggests that the rapid delivery of nutrients to the lower intestine enhances the stimulation of intestinal L cells that produce GLP-1, leading to improved insulin sensitivity. The 'upper intestinal hypothesis'[38] suggests that the exclusion of a short segment of upper small intestine from contact with ingested nutrients may result in reduced production of anti-incretins such as ghrelin, with subsequent improvement of glucose tolerance. It is, of course, highly plausible that both these mechanisms contribute to the anti-diabetic effects of bariatric surgery[39].

Whatever the ultimate mechanisms implicated in diabetes regression after bariatric surgery, this dramatic effect, as well as the growing prevalence of bariatric surgery interventions, provides a pool of patients that can be studied with the aim of identifying novel factors that may be implicated in T2DM development. The IT-Diab consortium is therefore recruiting a cohort of more than 600

obese diabetic and non-diabetic patients undergoing gastric banding or bypass surgery. Blood and tissue samples will be harvested from these patients at the time of surgery and during longitudinal follow-up over a period of up to five years. The profiling of gene and protein expression in these samples will provide valuable insight into novel therapeutic targets for T2DM.

Taken together, these two cohorts recruited by the IT-Diab consortium provide innovative and complementary clinical tools for the cross-validation of newly identified therapeutic targets in T2DM. In conjunction with cutting-edge translational technology, these approaches may thus provide new areas of research for the discovery and development of novel T2DM therapies.

Summary

The past 30 years have witnessed a revolution in diabetes management, with a move away from simple insulin treatment for glycemic control to improved understanding of the underlying mechanisms of the pathology, and the development of an impressive number of potential therapeutic approaches. Unfortunately, at the same time, sedentary lifestyles and the explosion of unbalanced dietary habits have led to the current obesity pandemic, with the worldwide obese population now estimated at 300 million. Due to the high association between obesity and T2DM, there is thus an ever-growing need to improve prediabetes and diabetes diagnosis and management. While treatment strategies have undeniably progressed, the International Diabetes Federation considers that many, if not the majority, of diabetic patients still have unmet medical needs.

Indeed, the benefit of aggressive HbA1c-lowering therapy has been questioned by major clinical trials such as ACCORD, ADVANCE and VADT, in which the intensive control of HbA1c levels had beneficial effects on microvascular diabetic complications, but did not reduce macrovascular disease or overall mortality[3]. It is thus now recognised that future anti-diabetic strategies should be designed to address multiple clinical endpoints related to the multifactorial nature of T2DM.

A wide range of different therapeutic approaches are being applied to tackle the multifactorial nature of T2DM, as discussed here, and the ClinicalTrials.gov website currently lists almost 1,000 active Type 2 diabetes trials worldwide. The inclusion of cardiovascular parameters in the study endpoints of these trials, together with the growing awareness of the importance of tackling cardiometabolic disease, including associated liver diseases, as a whole, means that the coming years hold great promise for the identification of novel therapeutic strategies for T2DM and its associated diseases. DDW

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