Review

2020 vision – An overview of prospects for diabetes management and prevention in the next decade

Chih-Yuan Wang a,*, David L. Neil b, Philip Home c

a Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
b Scientific Development Department, Content Ed Net, Taipei, Taiwan
c Institute for Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

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ABSTRACT

After a century of medical progress, people nowadays live longer with diabetes than ever before. However, current preventative approaches, compounded in part by increased life-expectancy, are failing to reduce the prevalence of diabetes. Cardiovascular sequelae account for many of the four million deaths annually attributable to diabetes. Evidence indicates that certain glucose-lowering medications can improve vascular outcomes in some people with type 2 diabetes, which, together with better understanding of using multiple therapies concurrently, offers opportunities for beneficial personalization of medication regimens. However, further well-designed long-term studies are needed to evaluate cardiovascular benefits and safety of new and older medications, particularly in users typical of everyday diabetes care. Although there are numerous other promising advances in pharmacotherapies and biotechnology, these will probably be unaffordable for most people with diabetes globally. Therefore, effective national public health approaches will be essential to reducing the incidence of diabetes and its associated burdens; these may entail politically controversial measures to change unhealthy lifestyle behaviours. Stakeholders could learn from past failures and emulate successes in other health-care initiatives. Without early action at all levels, we face a future in which approaching one-quarter of humans will have diabetes, with more than half afflicted during their lifetime.

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* Corresponding author at: Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, 7 Chung-Shan South Rd., Taipei 10051, Taiwan.
E-mail address: cyw1965@ntu.edu.tw (C.-Y. Wang).
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Before the 1920s, people diagnosed with diabetes succumbed fast, often as juveniles [3]. Insulin promised resurrection, yet even as Joslin hailed the first astounding ‘cures’, he cautioned that an ominous tide of obesity-related chronic disease was swelling [2]. Today, adults with type 2 diabetes (T2DM) outnumber those with type 1 diabetes (T1DM) nine to one, hundreds of millions worldwide use glucose-lowering medications, and the pandemic is overwhelming healthcare capacity [3–8]. Since 1980, successive estimates of the global prevalence of diabetes have surpassed earlier projections (Fig. 1, Supplementary Table S1), and its prevalence has not declined significantly in any country [7]. Although prevalence may be stabilizing in some countries, the global total may exceed 700 million by 2025, more than 10% of people [7]; the increase is most rapid in Africa and largest in Asia [6–8]. Estimated global healthcare spending on diabetes has more than tripled since 2003, with direct annual expenditure currently estimated at ≥USD825 million equivalent [4,7]. However, the health burden of diabetes is largely unknown – as yet, ‘only’ four million deaths per year are attributable to diabetes or its sequelae [3].

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.06.007.

Clearly, diabetes management must be substantially improved, with both wider access to healthcare and better care delivery [5]. How will contemporary developments shape the future therapeutic landscape, what impact might these have in diminishing the associated cost and health burdens – or in increasing them – and what issues may remain unresolved? International experts met in April 2016 to address this agenda; this commentary focuses on the evolution of glucose-lowering pharmacotherapy, potential applications of new and emerging technologies, and their implications for clinical practice in the 2020s. Our intention is to prospect the near-future clinical landscape, and we do not cover farther-distant technologies nor, inevitably, review each topic area in detail. Neither do we seek to address the important but essentially political issue that new technologies are usually expensive, which raises a barrier to access by the majority of people with diabetes, irrespective of their needs.

1. A prediction ... and a predicament

Before the 1920s, people diagnosed with diabetes succumbed fast, often as juveniles [3]. Insulin promised resurrection, yet even as Joslin hailed the first astounding ‘cures’, he cautioned that an ominous tide of obesity-related chronic disease was swelling [2]. Today, adults with type 2 diabetes (T2DM) outnumber those with type 1 diabetes (T1DM) nine to one, hundreds of millions worldwide use glucose-lowering medications, and the pandemic is overwhelming healthcare capacity [3–8]. Since 1980, successive estimates of the global prevalence of diabetes have surpassed earlier projections (Fig. 1, Supplementary Table S1), and its prevalence has not declined significantly in any country [7]. Although prevalence may be stabilizing in some countries, the global total may exceed 700 million by 2025, more than 10% of people [7]; the increase is most rapid in Africa and largest in Asia [6–8]. Estimated global healthcare spending on diabetes has more than tripled since 2003, with direct annual expenditure currently estimated at ≥USD825 million equivalent [4,7]. However, the health burden of diabetes is largely unknown – as yet, ‘only’ four million deaths per year are attributable to diabetes or its sequelae [3].

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2. Questions ongoing clinical trials can and cannot answer

2.1. Cardiovascular safety

Although most people with diabetes die from cardiovascular (CV) sequelae, early studies were not large enough to evaluate CV outcomes validly [9]; even the United Kingdom Prospective Diabetes Study (UKPDS) was underpowered at its endpoint [10], although longer-term follow-up showed reduced all-cause and diabetes-related death, as well as myocardial infarction for the sulfonylurea/insulin cohort [9,11]. Since 2008, when the United States (US) Food and Drug Administration (FDA) mandated CV safety studies as a licensing precondition, more CV outcomes trials (CVOTs) in T2DM have added to earlier data from UKPDS [10–12] and thiazolidinedione studies [13–15] (Table 1); results for dipeptidyl-peptidase-4 inhibitors (DPP-4i) [16–18]; glucagon-like peptide-1 receptor agonists (GLP-1RA) [19–22], sodium-glucose linked transporter-2 blockers (SGLT2b) [23,24], and insulins [25,26] have been reported, with others anticipated in 2018–2020.

The most compelling evidence so far for CV benefits associated with glucose-lowering has come from the LEADER [19] and SUSTAIN-6 [20] studies (liraglutide, semaglutide) and EMPA-REG-OUTCOME [23] and CANVAS [24] (empagliflozin, canagliflozin). However, glucose lowering is unlikely to account for any of the strong advantage for hospitalization for heart failure (HF) or lesser effects on overall major CV outcomes. The discordant results for exenatide may be real, or due to the study design [22]. Chronic kidney disease (CKD) is a major comorbidity of T2DM, culminating in the heavy burden of end-stage renal failure. Both SGLT2b studies suggest...
strong protection against renal disease progression [24,27], and other studies in people with T2DM and CKD are underway. A current concern is that SGLT2b’s have been associated with potentially life-threatening euglycemic diabetic ketoacidosis [28]. Other unresolved issues include possible class or drug-specific effects on bone metabolism, pancreatic inflammation, and toe amputations.

Recent studies have also begun to redress the lack of data on HF comorbid with T2DM, which increases a person’s mortality risk ten-fold [29]. Current evidence suggests that SGLT2b’s may be especially advantageous, presumably secondary to their hypovolaemic effect, although metabolic changes have been suggested [23,24]; in a large real-world T2DM cohort, incidence of HF and mortality risk were significantly lower among people newly initiated on SGLT2b’s versus other glucose-lowering drugs [30]. Although SAVOR-TIMI unexpectedly suggested that saxagliptin worsens HF [16], an outcome that was neither a primary nor secondary endpoint, and data for alogliptin are equivocal, there is no evidence that sitagliptin or other glucose-lowering medications, except thiazolidinediones, have harmful effects; further data for linagliptin are expected in 2018. An earlier contraindication for metformin was revoked [29]. Further long-term trials are needed for the many glucose-lowering medications without data in users with HF.

Unfortunately, the imperative to demonstrate acceptable CV risk as efficiently as possible means that CVOT cohorts are often unrepresentative of people receiving ambulatory diabetes care [9,18,21,23]; better-designed trials in more representative populations (eg, unrestricted for prior morbidity or age) and with longer follow-up and superiority as the outcome are needed to find out whether benefits observed in people with CV disease will extrapolate to those without. Until then, the potential longer-term risks and benefits will remain uncertain and there will be no answer to the question of precisely how much glucose-lowering therapy with newer agents reduces CV risk, and over what timeframe.

2.2. Choice and order of glucose-lowering medications

International guidelines generally recommend lifestyle changes and starting metformin as monotherapy at diagnosis or in the ensuing months, unless contraindicated or glycated haemoglobin (HbA1c) ≥9.0% (75 mmol/mol) suggests first-line dual therapy [31]. If HbA1c remains above the target level after 3 months, other medications are added sequentially...
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Medication</th>
<th>Study name/acronym</th>
<th>Outcomes assessed</th>
<th>Other cardiovascular</th>
<th>Clinicaltrials.gov ID [Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>UKPDS (sub-study)</td>
<td>Diabetes death/MI Stroke</td>
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<td>[12]</td>
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<tr>
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<td>Sulfonylurea/insulin</td>
<td>UKPDS (main study)</td>
<td>Diabetes death/MI Stroke</td>
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<td>[10]</td>
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<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>PROActive</td>
<td>MI/stroke/ACS/ endovascular surgery</td>
<td>MACE and components</td>
<td>NCT00174993 [13]</td>
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<td></td>
<td>Pioglitazone</td>
<td>TOSCA-IT</td>
<td>Death/MI/Stroke/ Revascularisation</td>
<td>Composite including HF hospitalisation/ endovascular surgery/silent MI/UA</td>
<td>NCT00700856 [14]</td>
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<td>Dipeptidyl-peptidase-4</td>
<td>Rosiglitazone</td>
<td>RECORD</td>
<td>CV hospitalisation/death MACE, HF</td>
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<td>Sitagliptin</td>
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<td>Composite MACE</td>
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<td>Alogliptin</td>
<td>EXAMINE</td>
<td>CV death/MI/stroke Hospitalisation for UF/UA/ revascularisation</td>
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<td>NCT00968708 [18]</td>
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<td>Linagliptin</td>
<td>CARMELINA</td>
<td>CV death/MI/stroke Hospitalisation for UF/UA/ revascularisation</td>
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<td>NCT01897532 [19]</td>
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<td></td>
<td>Liraglutide</td>
<td>LEADER</td>
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<td>NCT01179048 [20]</td>
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<td>Glucagon-like peptide-1</td>
<td>Semaglutide</td>
<td>SUSTAIN-6</td>
<td>CV death/MI/stroke</td>
<td></td>
<td>NCT01720446 [21]</td>
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<td>receptor agonist</td>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>CV death/MI/UA hospitalisation for UF/UA/ revascularisation</td>
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<td>NCT01147250 [22]</td>
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<td></td>
<td>Dulaglutide</td>
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<td>Hospitalisation for HF/UA/ revascularisation</td>
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<td></td>
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<td>Hospitalisation for ACS/UF/ revascularisation</td>
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<tr>
<td>Sodium-glucose linked</td>
<td>Empagliflozin</td>
<td>EMPA REG OUTCOME</td>
<td>CV death/MI/stroke</td>
<td>UA/HF hospitalisation</td>
<td>NCT01131676 [26]</td>
</tr>
<tr>
<td>transporter-2 inhibitor</td>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>CV death/MI/stroke</td>
<td></td>
<td>NCT01032629 [27]</td>
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<td></td>
<td>Dapagliflozin</td>
<td>DECLARE-TIMI-58</td>
<td>CV death/MI/stroke/ HF hospitalization</td>
<td></td>
<td>NCT01730534 [28]</td>
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<tr>
<td></td>
<td>Ertugliflozin</td>
<td>VERTIS CV</td>
<td>CV death/MI/stroke</td>
<td>Hospitalisation for UF/ revascularisation</td>
<td>NCT01986881 [29]</td>
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<td>Degludec</td>
<td>DEVOTE</td>
<td>CV death/MI/stroke</td>
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<td>NCT01959529 [31]</td>
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MI, myocardial infarction; ACS, acute coronary syndrome; MACE, major adverse cardiovascular events; HF, heart failure; UA, unstable angina.
Although more effective prevention is crucial to abating hyperglycaemia at high CV risk being managed in primary care [38]. The Restoring Insulin Secretion (RISE) study is investigating whether obesity-reducing surgery, or glucose-lowering with metformin alone or combined with insulin glargine or liraglutide, can slow or reverse progressive islet β-cell dysfunction in incipient T2DM [39]. RISE is also intended to determine whether T2DM pathogenesis and progression are similar in adults and children. However, it will remain uncertain whether or not interventions evaluated in prevention studies can be applied in clinical practice.

### 3. New management paradigms for the 2020s

#### 3.1. Beyond ‘treat-to-failure’

Hyperglycaemia involves multiple interacting metabolic processes, including increased hepatic glucose production, deficient insulin secretion and action, excess glucagon secretion, and a diminished incretin effect, modulated by increased lipolysis and abnormal neurotransmission, among others [40]. Different pharmacotherapeutic classes target particular aspects of this nexus but none deteriorating islet β-cell function, which starts before diabetes develops and continues inexorably thereafter [41]; indeed, only thiazolidinediones have evidence of any efficacy in this regard [33]. Among 1799 first-time metformin users who achieved HbA1c < 7.0% (<53 mmol/mol), 42% had secondary failure within 2–5 years, only 30% of whom were prescribed a second medication; although failure to maintain target was less likely among those using metformin within 3 months of diagnosis, the rate was still 12% per year [42]. Until recently, metformin was typically partnered with a sulfonylurea, which are inexpensive; however, the strong initial effect of these medications is lost by 12 months, with progressive β-cell failure at a rate higher than metformin thereafter [33,40].

There is a strong rationale for abandoning the conventional ‘treat-to-failure’ approach in favour of a paradigm in which drug combinations with complementary mechanisms capable of addressing multiple underlying pathophysiological defects and normalizing glucose levels with low risk of hyperglycaemia are begun earlier (Table 2) [31,40,43,44]. Such a regimen is unproven, but might include agents that are insulin sensitizing and anti-atherogenic (eg, metformin, thiazolidinedione), islet β-cell preserving (thiazolidinedione), and that

<table>
<thead>
<tr>
<th>Table 2 – Desirable attributes of glucose-lowering medications.</th>
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<tr>
<td>• Lower blood glucose level effectively (at least as well as lifestyle intervention)</td>
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<tr>
<td>• Carry low risk of hypoglycaemia</td>
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<tr>
<td>• Do not result in weight gain</td>
</tr>
<tr>
<td>• Evidence for amelioration of microvascular and macrovascular risk</td>
</tr>
<tr>
<td>• Additional benefits on other cardiovascular outcomes, lipid profile, or preserving islet β-cell function</td>
</tr>
<tr>
<td>• Durable glucose-lowering effect/prevention of islet β-cell decline</td>
</tr>
<tr>
<td>• Well-tolerated, with minimal toxicity or adverse effects</td>
</tr>
<tr>
<td>• Safe in long-term use, with no need for safety monitoring</td>
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<tr>
<td>• Complementary to other glucose-lowering classes, or even synergistic</td>
</tr>
<tr>
<td>• Mechanism remedies underlying pathophysiological defects</td>
</tr>
<tr>
<td>• Priced comparably with established medications that are widely available</td>
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</table>

modulate caloric intake or loss (GLP-1RAs, SGLT2b’s) [31,40]. Successful outcomes of some GLP-1RA and SGLT2b CVOTs [19,23,24], make these further candidates for early combination approaches.

3.2. Optimizing combination therapy

Although up-front combination therapy is often used and successful in therapeutic areas such as cancer and infectious disease, current mainstream T2DM guidelines do not endorse this approach [31]. Besides avoiding unnecessary polypharmacy if monotherapy suffices, another barrier may be concern about adverse effects – nearly all classes of oral glucose-lowering medications cause significant problems, ranging from gastrointestinal intolerance and weight gain, through symptomatic hypoglycaemia, fractures, and genitourinary infection, to severe hypoglycaemia and lactic acidosis [45]. Low-dose combination therapies have been suggested as a pragmatic approach to minimizing side effects. For example, the Canadian Normoglycemia Outcomes Evaluation study, found that people with impaired glucose tolerance who received half-maximal doses of metformin plus rosiglitazone had 26% lower absolute risk of developing T2DM versus placebo [45]. Another rational option, widely available in fixed combinations, would be metformin plus a DPP-4i, as the latter are unusually well tolerated and achieve durable HbA1c reduction [44]. Other possibly advantageous combinations include a SGLT2b plus metformin or a DPP-4i, or a GLP-1RA combined with either metformin and a thiazolidinedione [46], or insulin [32]; however, there are many rational possibilities [44].

3.3. Insulins present and future

Due to progressive islet β-cell failure [41], most people with T2DM eventually need insulin therapy if they are to control hyperglycaemia. A century of development has produced truly long-acting insulins, some now with flat 24-hour profiles [47,48]. Once-daily basal insulin thus enabled insulin therapy to be started more timely [49], traditionally followed by adding prandial insulin. However, fixed or variable ratio insulin/GLP-1RA combinations that are highly efficacious, with less hypoglycaemia or weight gain, are now entering routine use, usually once-daily or even once-weekly [49,50]; these are used when starting insulin, or often instead of adding prandial insulin to basal insulin. Though expensive, these approaches are rapidly becoming more widespread, with meal-time insulin only introduced later. Weekly GLP-1RAs are already proving commercially successful and weekly insulins, though posing a bigger pharmaceutical challenge, are anticipated, potentially enabling weekly combination injection.

Diverse developments in pharmaceutical and injection depot technologies are also enabling more physiological prandial insulin profiles, with more rapid onset [49]. These approaches are being supplemented with continuous glucose monitoring, which is now making clinical inroads after 50 years of development, together with various insulin dose advisor concepts, many based on smart phone technology, although common standards are lacking. Some systems are linked to insulin pumps, in forms that include low-glucose insulin suspend, dual insulin/glucagon delivery, and basal only devices for T2DM, all moving towards full closed-loop control. However, unresolved problems of intravenous sensing and infusion, and the barriers imposed by time-lag, subcutaneous sensing and insulin absorption, mean that normoglycaemia remains unattainable [51].

Other products anticipated after 2020 include glucose-responsive insulins [52], regenerative insulin secretion by engineered self- or stem-cell-derived β-cells, and insulin-linked single peptides including GLP-1RA and other glucagon-related molecules. Equally or more problematic are oral insulin delivery, which must overcome erratic absorption and poor bioavailability, and small-molecule insulin analogue agents; these fail to match physiological insulin profiles, and insulin analogues may send undesirable downstream cellular growth signals.

4. The nutritional nexus

4.1. Partners in health crime

Diabetes had been linked to obesity long before Joslin published seminal epidemiological evidence 100 years ago [1,53]. Asians appear especially susceptible to the adverse effects of calorie surplus, developing T2DM at a higher rate than similarly heavy Europids, probably reflecting their tendency to central and hepatic rather than peripheral adiposity. Besides rapid socioeconomic development in Asia driving an obesogenic nutritional transition, metabolic genetic differences probably make an important contribution as well [6]. Although many obese people have a cluster of metabolic abnormalities that increase their risk of diabetes and CV disease, some are relatively ‘metabolically normal’ and may therefore require less aggressive preventive interventions than others [54]. New research is elucidating the pivotal role of adipose tissue in mediating the beneficial effects of weight loss and exercise, which are essential to non-pharmacologic intervention. Changing body weight alters adipose tissue gene expression; weight gain increases lipogenic capacity (in ‘metabolically-normal obese’ people) [54], while lipid flux pathways are up-regulated and lipid synthesis down-regulated in step with weight loss [55]. Pre-clinical studies are also revealing a previously unrecognized role for adipose tissue in mediating the benefit of physical activity in improving glucose homeostasis, beyond known effects on muscle [56].

Randomized studies have shown that low-carbohydrate diets achieve more weight loss than low-fat diets [57], while Mediterranean-style or high-protein diets are more effective in controlling glycaemia and improving CV risk markers in T2DM [58]. Very low calorie intake can even reverse key metabolic abnormalities underlying T2DM within days, through depleting pancreatic and hepatic lipid stores which are strongly implicated in its aetiology [59,60]. In a large-scale prospective UK study, structured weight management supervised in routine primary care upon withdrawal of glucose-lowering pharmacotherapy, achieved remission at 12 months in nearly half of people with T2DM diagnosed within the past 6 years [61]. The results suggest that
remission and its considerable associated benefits is a realistic and potentially cost-effective health service objective. Although calorie restriction progressively improves insulin sensitivity, islet β-cell function and metabolic functions in multiple organs [55], the cardioprotective effect remains uncertain; in the Look AHEAD study, around 10 years of intensive weight control mitigated individual CV risk factors but did not significantly reduce CV morbidity or mortality, perhaps reflecting poor longer-term adherence to dietary change [62].

4.2 Pharmacological and surgical weight-loss

Since lifestyle modification alone seldom sustains weight control over the long-term, additional medical intervention appears desirable; however, there is an unmet need for better options [63]. Though the US FDA has approved 15 anti-obesity drugs since the 1940s, several were withdrawn due to adverse effects. Until recently, orlistat, which is poorly-tolerated and unsatisfactorily efficacious in promoting weight loss but has been shown to reduce the incidence of T2DM, was the only drug approved for long-term therapy [63,64]. Newer agents, including phentermine/topiramate, lorcaserin, bupropion/naltrexone and high-dose liraglutide, now offer alternatives for suitable patients; however short-term efficacy is modest, and long-term efficacy and safety data are awaited [63,64]. Semaglutide appears particularly efficacious [65]. Prospective therapies include combination peptides, components including GLP-1RAs, peptide YY, and glucagon receptor agonists, and oxyntomodulin derivatives [66]. For now, bariatric surgery is the most effective way to achieve clinically-meaningful long-term weight loss; this can control glycaemia and reverses diabetes in some people, potentially reducing CV mortality [64,67], but is obviously not a feasible population-level solution.

4.3 Influence of gut microbiota

Manipulating the gut microbiota offers a potentially non-pharmacological, non-invasive intervention approach [68]. Recipients of faecal transplants from obese donors gain weight [69], whereas intestinal microbiota transplants from lean donors to people with metabolic syndrome improved insulin sensitivity [70].

5. Biotechnology beckons

5.1 Integrating the ‘omics

‘Omics research has potential to drive future advances in precision medicine, in which molecular signatures can be reverse-translated via preclinical and clinical studies to reveal disease mechanisms responsive to new therapeutic targets. For example, integrating genetics, epigenetics, and gene expression profiling with metabolomics has unveiled the ubiquitin proteasome system and endoplasmic reticulum stress as mechanistic links between short-chain dicarboxylic-carnitine levels and CV disease [71]. Genome-wide association studies identified a common single-nucleotide polymorphism in SLC30A8 associated with significantly increased risk for developing T2DM. SLC30A8 encodes an islet β-cell-specific zinc transporter involved in insulin secretion, and subsequent high-throughput sequencing showed that SLC30A8 loss of function mutations protect against T2DM, suggesting that inhibiting this pathway may have therapeutic potential [72].

Metabolomic profiling has confirmed that elevated levels of branched-chain amino acids (BCAA) are implicated in insulin resistance and strongly prognostic for developing T2DM [73]. BCAA levels are influenced by multiple interacting factors, including diet, genotype, metabolic processing, and the gut microbiome, and levels fall with weight loss [74,75]; consequently, they are responsive to various therapeutic interventions, including gastric bypass surgery, certain pharmacological agents (e.g., sulfonylureas), and lifestyle interventions [73–76]; in the Weight Loss Maintenance trial, BCAAs and related metabolites were associated with improved insulin resistance [74].

5.2 Applications and opportunities

More than 100 other genetic variants associated with the risk of developing T2DM have been reported. Although most have too little effect individually to enhance clinical risk assessment [77], such markers can complement each other and metabolomics to provide greater predictive accuracy than conventional risk factors, especially in younger people (<50 years) [78]. Individual genetic risk analysis can also help in discriminating T1DM from T2DM in young adults – an increasing clinical need [79]. When it comes to targeted prevention, high absolute individual risk, rather than relative genetic risk, is most important, highlighting the need for universal approaches [80]; nevertheless, ethnic-specific polymorphisms with much greater impact may help to target pre-emptive intervention to susceptible individuals [81]. For example, a TBC1D4 mutation increases the risk of T2DM ten-fold in Greenland Inuit [82], and an HNF1A variant carried by 2% of Mexicans increases their risk five-fold [83]. SLC16A11 mutations, which are also very common in Latin America, increase the risk of early-onset T2DM and account for up to 20% of the increased risk in Mexico [84].

Genetic testing may also have a role in predicting who might respond best to lifestyle or pharmacological interventions; for example, the success of non-pharmacological weight loss varies with polymorphism in the MC4R gene [81], and different susceptibility variants cluster into aetiological groups that correspond to primary effects on insulin sensitivity, reduced insulin secretion and fasting hyperglycaemia, and defective insulin processing [85]. Metformin monotherapy fails to sustain glycaemic control in half of children and adolescents with T2DM [86], partly due to intolerance but likely due also to genetic determinants of poorer drug response [87].

5.3 Cell therapy ventures

Progress continues apace in the elusive quest to restore endogenous insulin secretion, notably in T1DM [88]. Though advances in pancreatic tissue transplantation have made this
expedient for some people, this has inherent limitations of shortage of donor tissue and the need for subsequent immunosuppression [88,89]. Stem-cell engineering breakthroughs are realizing the promise of in vitro mass-production of glucose-responsive, insulin-producing cells from human pluripotent stem cells (hPSC) [90,91]. Functionally equivalent to islet β-cells, such cells reversed diabetes in mice within 40 days [90]; others have since reported longer-term survival and function in microencapsulation devices implanted into immunocompetent mice [92]. Encapsulation materials are engineered to fend off immune rejection by excluding host cells, as well as confining transformed cells with malignant potential, while allowing ingress/egress of nutrients and cell products [88,89]. However, it is currently uncertain how the cells will mature in situ, how long they will survive, how many are needed for insulin-independence, and how the body reacts to such devices. Possible solutions to preserving the functional integrity of hPSC-derived implants include pre-vascularized devices, anti-inflammatory and/or chemokine coatings, re-engineered self-cells, and immunotherapy to induce immune tolerance [88,89,93]. Following proof-of-concept [94], first-in-human trials to evaluate the efficacy and safety of implanting encapsulated hPSC-derived pancreatic endoderm progenitors into adults with T1DM may provide preliminary answers (https://clinicaltrials.gov/ID: NCT02239354, NCT02939118, NCT03163511, NCT03162926).

6. Whither forecast

How will the diabetes therapy landscape look in the 2020s? Improving vascular and safety outcomes will entail integrating pharmacological, biomechanical and behavioural approaches; in particular, technologies proven to prevent diabetes and vascular disease must be deployed diligently to all who might benefit. Trends towards individualized and precision medicine targeting underlying pathological components of diabetes, should enable longer-term, more physiological, glycaemic control, with fewer undesirable effects – perhaps even reversal of T2DM. There will also be continued growth of using existing therapies concurrently, basal insulin, and glucose-lowering medications with beneficial additional vascular effects, such as GLP-1RAs and SGLT2b’s. Glycaemic targets will probably be better defined and individualized, and evidence from large-scale long-term clinical trials will continue to change guidelines. CVOTs over the past decade have steadily raised the bar for assessing CV safety, while positive findings from EMPA-REG-OUTCOME [23], CANVAS [24] and LEADER [19] suggest that their respective medications are not just options but should be adopted in clinical practice, particularly in groups representative of those studied. Other studies widening the applicable populations are underway. However, there remains a major unmet need to more rigorously evaluate the CV effects and wider safety of all new medications, as well as other clinically-relevant outcomes including microvascular complications, preservation of islet β-cell function, improved metabolic profile, cost effectiveness, and not least quality of life. The issue of ketoacidosis associated with SGLT2b’s [28] (perhaps more so with SGLT1/2b’s), needs further investigation, particularly in T1DM [95] – professional and patient education may, but might not, lessen the risk of this potentially fatal complication.

6.1. Turning Joslin’s tide

Importantly, an unmet need for inexpensive but efficacious drugs and lifestyle modification will persist; cutting-edge pharmacotherapies, biotechnologies, and risk-assessment techniques benefit only people with access to state-of-the-art health-care services, and are likely to remain beyond the reach of the majority of people with diabetes in resource-poor countries who suffer the heaviest global burden [5]. Accordingly, most people will remain reliant on conventional glucose-lowering medications and those coming off patent. Besides, medicine alone cannot turn Joslin’s tide; it will be impossible to substantially reduce the incidence of diabetes without public health initiatives that cement enduring lifestyle-changes [5,7]. This inescapable conclusion deserves much more thorough analysis beyond the scope of this broad overview, particularly concerning the socioeconomic and political forces driving the diabetes epidemic.

Joslin, who deplored obesity, wrote in 1921, “...it is proper at the present time, to devote attention not alone to treatment, but still more ... to prevention” [53]. His maxim is truer now than ever, but how to achieve and fund this is still unclear. The apparently obvious solution of changing unhealthy behaviour is a difficult undertaking [96]. Although population-based interventions have reduced hard outcomes over periods as long as 40 years [97] and school-based anti-obesity programmes have shown some success [98,99], escalating incidence of T2DM globally attests to the failure of conventional approaches, and better alternatives are clearly needed, perhaps including taxing convenience foods and high-sugar drinks [5]; however, emerging evidence suggests that this is no panacea [100]. Although such measures can be politically controversial, the approach has had some success for tobacco and alcohol, while another relevant initiative involved removing soft-drinks machines from schools. The battleground is a human constitution hardwired to endure prehistoric privations and ill-adapted to cope with incessant bounty, while adult habits seem programmed by childhood experience. A subtler approach that considers obesity the natural consequence of modern urban environments and persuasive marketing rather than weak willpower, and promotes incrementally healthier lifestyle choices, may be more fruitful than admonitions to eat less [96].

Facing this immense challenge, what are the most pressing priorities? Low-hanging fruit appear to be school education, and expanded access to existing diagnostic and therapeutic modalities, which must be applied more assiduously and effectively [5]. A key missing element is universal implementation of pragmatic, cost-effective, awareness raising and prevention programs that can change unhealthy lifestyle behaviours at the population level [5], for which there are models [61,97,98] and without which rising prevalence of diabetes cannot be reversed [5,7]. It is incumbent on stakeholders to work together to emulate other successes, such as with tobacco control and sun/skin safety, as well as to learn from earlier failures. Without action at all levels, we face a
foreseeable future in which approaching one quarter of humankind may have diabetes, and half will suffer during their lifetime – a 21st century scourge rivalling any in history.

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Author contributions

CYW conceived the review format and content, and analysed and interpreted source materials. PH and DLN supplied, analysed and interpreted source materials. DLN wrote the manuscript, which CYW and PH revised critically for important intellectual content; CYW, DLN, and PH approved the final version submitted and take responsibility for its integrity and accuracy.

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