Trends in Endocrinology & Metabolism

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Opinion

Prevention and Treatment of Type 2 Diabetes: A Pathophysiological-Based Approach

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Prediabetes affects approximately 40% of American adults. Randomized trials report that a proportion of individuals with prediabetes develop diabetes despite caloric restriction, physical activity, and/or when treated with metformin, the first-line medication for patients with type 2 diabetes mellitus (T2DM). Currently, there are no valid predictors of the effectiveness of these measures in determining who will and who will not progress to the T2DM state. Few studies have examined the clinical and phenotypic predictors of better and worse glycemic response to lifestyle interventions and metformin in prediabetes and diabetes. Further studies incorporating 'omic' approaches to discover novel markers of phenotypes and treatment effectiveness may pave the way to personalizing the treatment of prediabetes and diabetes.

Highlights

Prediabetes is common and is a significant risk factor for developing not only diabetes, but also micro- and macrovascular disease, fatty liver, and cancer.

Prediabetes is characterized by heterogeneous defects in insulin sensitivity and insulin secretion, which are themselves determined by genetic and other factors.

Many individuals with prediabetes progress to T2DM despite lifestyle intervention and treatment with metformin.

Phenotypic predictors of better and worse responders to lifestyle interventions or metformin have been suggested, but findings are inconsistent.

Prediabetes: Globally Prevalent Condition with Poor Treatment Outcomes

Prediabetes is a state of dysglycemia that precedes the development of T2DM. It is a risk factor for cardiovascular disease, fatty liver, renal, ophthalmic and neuropathic disease, cognitive dysfunction, and cancer [1]. The prevalence of prediabetes depends on the definition used to diagnose it (**prediabetes diagnosis**; see Glossary), and on the population studied. Prevalence in adults is reported at 38% in the USA [2] and 35.7% % in China [3]. While not everyone with prediabetes will develop diabetes, the annual rate of progression from prediabetes to diabetes is high. In the US Diabetes Prevention Program Outcomes Study (DPPOS), annual rate of progression was 11% [4] and, in a population of Asian Indians, annual progression was 13.4% [5] in participants with **impaired fasting glucose** (IFG) and/or **impaired glucose tolerance** (IGT) at baseline.

The current American Diabetes Association (ADA) guideline for management of individuals found to have prediabetes recommends an intensive behavioral lifestyle intervention, aiming to achieve and maintain a 7% body-weight loss and increase moderate-intensity physical activity to at least 150 min a week [6]. However, weight-loss goals are difficult to achieve and are even harder to maintain, with almost 80% of the lost weight regained within 5 years [7].

Pharmacological interventions to prevent diabetes in individuals with prediabetes are particularly recommended in individuals under 60 years of age, in those with a body mass index (BMI) $\geq$35 kg/m^2, in women with a history of gestational diabetes, and in individuals with an elevated hemoglobin A1c (HbA_{1c}) despite lifestyle changes [6]. Metformin, an oral biguanide, the first-line treatment of patients with newly-diagnosed T2DM, is the pharmacological choice for preventing diabetes in individuals with prediabetes. Metformin was first licensed as an antihyperglycemic medication 60 years ago. Its exact mechanism of action is still not clear and is intensively investigated [8]. Metformin is an ideal medication to initiate for diabetes

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prevention, due to its excellent safety profile (lack of hypoglycemia), neutral to marginally beneficial effect on body weight, modest evidence of cardioprotection, and low cost [9]. However, numerous studies suggest variability in the glycemic response to metformin, and poor response is common [10–12].

Here, we summarize the literature describing poor response to lifestyle interventions and metformin in individuals with prediabetes and diabetes. We also discuss the possible underlying predictors of poor response and how detailed phenotyping and developing 'omic' approaches may pave the way to the appropriate selection of medication to prevent progression from prediabetes to diabetes, and for more individualized treatment of frank T2DM.

Poor Response to Pharmacotherapy and Lifestyle Interventions in Diabetes

Clinical practice, backed by randomized clinical trials, suggests that monotherapy with diabetes medication fails to achieve glycemic goals in a large proportion of patients with T2DM. For example, in a double-blind, randomized, controlled clinical trial of >4000 individuals with newly diagnosed T2DM, Kahn and colleagues reported that 5 years of monotherapy with rosiglitazone, metformin, or sulfonylurea did not achieve glycemic goals in 15, 21, and 34% of patients, respectively [10]. Similarly, analysis of treatment response to metformin and sulfonylurea in a subcohort of the Genetics of Diabetes and Audit Research Tayside Study (GoDARTS) of treatment-naïve individuals with T2DM, suggested that 42% and 49% of sulfonylurea- and metformin-treated individuals, respectively, failed to achieve the HbA_{1c} target [≤7% (53 mmol/mol)] within 1 year of treatment initiation, despite good adherence to the medication [11]. Furthermore, while the short-term benefits of caloric restriction and exercise on whole-body glucose regulation are well established, even with modest weight loss [13], patients with T2DM in the Action for Health in Diabetes (Look AHEAD) trial who lost weight through caloric restriction and increased physical activity, were not better protected from cardiovascular events compared with the control arm over 9.6 years [14].

Phenotypic Predictors of Poor Response to Lifestyle and Metformin Interventions

Categorical analysis of subcohorts into better- and worse-glycemic responders to lifestyle and metformin interventions provides some clues to phenotypic predictors of glycemic response in prediabetes and diabetes (Table 1). Early interventions in prediabetes have been trialed in the Diabetes Prevention Program (DPP) [15], with a follow-up analysis in the DPPOS [4], and in the Diabetes Prevention Study [16]. Primary outcome measure was T2DM diagnosis.

Lifestyle interventions were similarly effective in the DPP and the Finnish Diabetes Prevention Study in preventing diabetes [15,16] and, when trialed against metformin, lifestyle intervention was more effective in preventing diabetes at 3 years (58% versus 31% risk reduction, Table 1). Yet, 14% of the lifestyle intervention-adherent participants developed diabetes at 3 years [12]. Progression to diabetes in participants randomized to the lifestyle intervention was predicted by higher BMI, fasting plasma glucose (FPG), serum triglycerides, and, paradoxically, by greater physical activity engagement before the randomization [12]. Prevention of diabetes with lifestyle intervention was most effective in individuals with lower 2-h plasma glucose (PG) during an oral glucose tolerance test (OGTT, Table 1). In the Finnish Diabetes Prevention Study, older age predicted better glycemic response to energy restriction and exercise; baseline anthropometry, glycemic status (FPG, 2-h PG during 75-g OGTT) and surrogates of insulin resistance (fasting insulin and **homeostatic model assessment of insulin resistance,** HOMA-IR) did not predict the glycemic response to the intervention [16] (Table 1).

Glossary

Genome-wide association studies (GWAS): observational studies investigating relationships between genome variations (single nucleotide polymorphisms, SNPs) that occur more frequently in humans with a particular disease or clinical traits in large cohorts of individuals. Data generated from GWAS identify genes that may contribute to a person's risk of developing a certain disease.

Homeostatic model assessment of insulin resistance (HOMA-IR): a surrogate measure of insulin resistance based on fasting plasma glucose and insulin, calculated using Equation I:

$$Fasting\ glucose\left(\frac{mg}{dL}\right) * Fasting\ insulin\left(\frac{mU}{L}\right)/405 \quad [I]$$

Increased HOMA-IR corresponds with increased insulin resistance.

Impaired fasting glucose (IFG): fasting PG concentration 100–125 mg/dL (5.6–6.9 mmol/L).

Impaired glucose tolerance (IGT): 2-h PG during 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L).

Insulin sensitivity index (ISI): marker of insulin resistance based on PG and insulin concentrations at fasting and during 75-g OGTT, calculated using Equation II:

$$\frac{10000}{\sqrt{Fasting\ glucose \times Fasting\ insulin \times (mean\ glucose \times mean\ insulin\ during\ OGTT)}} \quad [II]$$

Insulinogenic index: marker of insulin secretion based on plasma glucose and insulin concentrations at fasting and 30 min after oral ingestion of 75 g glucose, calculated using Equation III: (*Insulin at 30 min –Insulin at fasting*)/(*Glucose at 30 min –Glucose at fasting*) [III].

Metformin intolerance: some patients (up to 25%) treated with metformin experience varying degrees of gastrointestinal intolerance, which may include abdominal cramps, nausea, and vomiting.

Normal glucose tolerance (NGT): fasting PG <100 mg/dL (5.6 mmol/L) and 2-h PG during 75-g OGTT <140 mg/dL (7.8 mmol/L) and HbA_{1c} <5.7% (39 mmol/mol).

Table 1. Summary of Interventional Studies where Diabetes Risk Reduction Stratification is Available in Cohorts with Prediabetes

Study [Cohort Size (*N*), Average Length of Follow-Up)	Intervention and Design	Primary Outcome	Average Outcome	Risk Reduction in Better and Worse Responders[a]	Refs
Diabetes Prevention Program (*N* = 3234, 2.8 years)	Standard lifestyle recommendations + metformin 850 mg BID	T2DM (FPG ≥7.0 mmol/L or PG ≥11.1 mmol/L 2-h post 75-g OGTT)	7.8 cases/100 person-years (31% reduction versus placebo)	Metformin Better responders: Higher BMI (≥35 kg/m^2): 53% reduction Elevated FPG (6.1–6.9 mmol/L): 48% reduction Younger (24–44 years old): 44% reduction Worse responders: BMI 22–30 kg/m^2: 3% reduction FPG 5.3–6.1 mmol/L: 15% reduction Older (≥60 years old): 11% reduction	[18]
	Intensive lifestyle modification aiming at 7% weight loss through energy restricted, low-fat diet with ≥150 min of moderate-intensity physical activity		4.8 cases/100 person-years (58% reduction vs. placebo)	Intensive lifestyle Better responders: Lower PG 2-h post 75-g OGTT (7.8–8.5 mmol/L): 76% reduction Worse responders: Higher PG 2-h post 75-g OGTT (9.6–11.1 mmol/L): 50% reduction	[15]
	Standard lifestyle recommendations + placebo		11.0 cases/100 person-years		
Finnish Diabetes Prevention Study [*N* = 522, 3.2 years mean (4 years median), European population]	Lifestyle intervention aiming at ≥5% weight loss (dietary fat intake ≤30% of total energy intake, fiber intake ≥15 g/1000 kcal, moderate exercise ≥30 min/day) Control (general verbal and written information about diet and exercise)	T2DM (FPG ≥7.8 mmol/L or PG ≥11.1 mmol/L 2-h post 75-g OGTT) on two consecutive tests	Weight loss: Lifestyle: 4.2 ± 5.1 kg Control: 0.8 ± 3.7 kg Diabetes risk reduction: Lifestyle: 4.1/100-person years (58% versus control) Control: 7.1/100-person years	Better versus worse responders: Older individuals achieved best risk reduction from intervention [>61 y HR 0.36 (0.17–0.80), 51–61 y - HR 0.49 (0.26–0.93), <51 y - HR 0.77 (0.44–1.38)], all versus control, P_{trend} = 0.039, $P_{interaction}$ = 0.013) Effect of intervention on diabetes risk reduction not affected by baseline BMI, WC, glycemic status (FPG, PG 2-h post 75-g OGTT) and surrogates of insulin resistance (fasting insulin or HOMA-IR)	[16,51]
Subcohort of Tübingen Lifestyle Intervention Program study (*N* = 120, 9 months)	Caloric restriction and moderate exercise intervention aimed at achieving weight loss >5% Open label	Normal glucose tolerance	45% of participants reverted to normal glucose tolerance	Better responders: Less complicated individuals with prediabetes (lesser degree of insulin resistance and β cell dysfunction with lower liver lipid) Worse responders: Individuals with insulin secretory failure, worse insulin resistance and nonalcoholic fatty liver disease	[17]

[a]Risk reduction versus placebo or control is reported when available.
Abbreviations: BID, twice daily; FPG, fasting plasma glucose; HR, hazard ratio; OGTT, oral glucose tolerance test; PG, plasma glucose; WC, waist circumference.

In a subcohort of the Tübingen Lifestyle Intervention Program (TULIP), Stefan and colleagues [17] reported that, in response to 9 months of energy restriction and moderate exercise intervention aiming to achieve a 5% weight loss, 55% of the cohort did not revert to **normal glucose tolerance** (NGT). Even in individuals whose body fat mass decreased the most, 40% did not revert to NGT [17]. Better-controlled participants (i.e., participants who had a lower degree of β cell dysfunction, insulin resistance, and fatty liver) were more likely to revert to NGT (Table 1) [17]. In a post-hoc analysis of the DPP, regression to NGT at 3 years with the lifestyle intervention was predominantly predicted by achievement of a substantial (5%) weight loss after 6 months of the intervention [12].

Nutrigenetics: the inclusion of (selected) genetic information for tailoring nutritional interventions in individuals who are overweight or obese, or have metabolic disease.
Prediabetes diagnosis: participants without a prior diabetes diagnosis but found to have IFG and/or IGT

and/or HbA_{1c} 5.7–6.4% (39–47 mmol/mol).

Metformin treatment prevented 31% and 18% of diabetes cases relative to placebo on average, at 3 and 15 years of treatment in the DPP and DPPOS cohorts, respectively [18]. Notably, large variability in diabetes risk reduction with metformin in the DPP has been documented [18], with 21% of the adherent participants developing diabetes at 3 years [12].

Generally, adherent, younger participants, with higher BMI and FPG responded significantly better to metformin compared with older individuals with lower BMI and FPG (Table 1) [18]. In a recent post-hoc analysis of the DPP data, older age, smoking, history of polycystic ovarian disease, family history of diabetes, higher FPG, and higher fasting triglycerides predicted greater risk of progression to diabetes [12].

In summary, nonresponse to lifestyle and metformin interventions in prediabetes and diabetes is common. Some phenotypic characteristics may explain poor response, but inconsistencies exist in the literature and the phenotypic readouts that predict a better or worse response remain unclear.

Diverse Phenotypes in Prediabetes and Diabetes: Insulin Resistance and β Cell Dysfunction

Insulin resistance and β cell dysfunction are the key etiological determinants of prediabetes and diabetes. Transition from NGT to IGT to overt T2DM is characterized by a concurrent deterioration in whole-body insulin resistance and insulin secretion [19,20]. Retrospective analysis of individuals developing T2DM over 18 years in the Whitehall II cohort study, revealed distinct trajectories of whole-body insulin resistance and β cell function in individuals found to have T2DM based on elevated FPG versus elevated 2-h PG during the 75-g OGTT [21]. Before diagnosis, insulin sensitivity (**insulin sensitivity index,** ISI) declined more rapidly in patients found to have diabetes based on the 2-h PG during the OGTT compared with those found to have diabetes based on elevated FPG alone. By contrast, β cell function was substantially reduced before diagnosis in the subgroups found to have diabetes with elevated FPG, but remained relatively stable throughout follow-up in individuals found to have diabetes based on isolated elevated 2-h PG during the OGTT [21]. Moreover, there is a range of phenotypic variation in the degree and site of insulin resistance in prediabetes. Muscle and liver insulin resistance are significantly associated with each other in cohorts of nondiabetic overweight and obese individuals [22,23]. However, while some people with obesity present with insulin resistance in both muscle and liver, others exhibit single-organ insulin resistance in muscle or liver, while maintaining relative insulin sensitivity in the other organ [22].

These findings suggest that dysglycemia presents in diverse phenotypes. While diagnosing IFG and IGT requires relatively simple blood tests (fasting and 2 h after oral glucose load), the clinical efficacy of preventing diabetes or treating patients with diabetes effectively based on these relatively crude measures requires further investigation. Detailed metabolic phenotyping with measurement of the degree of whole-body insulin resistance (e.g., using the ISI) and insulin secretion (e.g., using the **insulinogenic index**) with imaging techniques, and evaluating abdominal fat distribution and deposition, are likely to more reliably identify the prediabetes and diabetes phenotypes and are feasible in fairly large cohorts [1,22]. Nevertheless, direct measurement of liver and muscle insulin resistance and β cell function involves long and expensive protocols, which are only feasible in relatively small cohorts. Therefore, identifying the underlying insulin resistance and β cell dysfunction phenotypes by sets of accessible markers may be important for therapeutic decision making. For example, differential plasma lipidomic signatures have been found in insulin-resistant and insulin-sensitive phenotypes of human obesity [24,25]. Other reported circulating metabolomic markers of metabolic disease

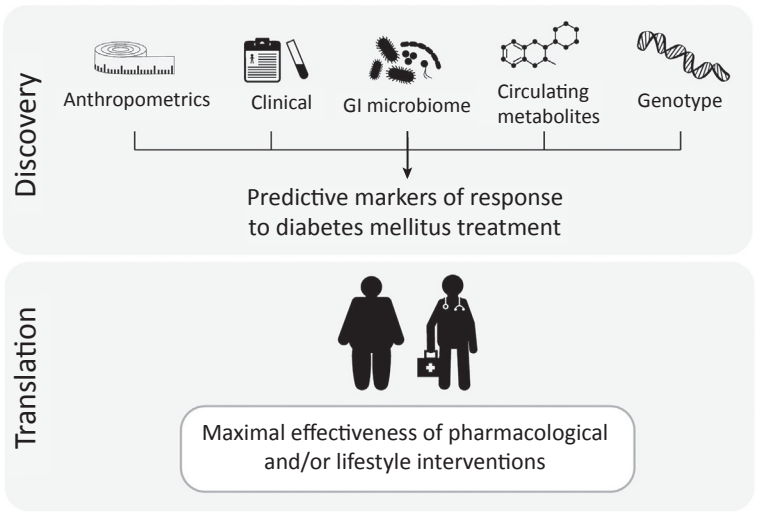

Figure 1. Towards Personalizing Management of Patients with Prediabetes and Type 2 Diabetes Mellitus. Therapeutic decision making in a person with prediabetes or diabetes may be aided by supplementing the individual's personal and clinical data (e.g., ethnicity, family and personal history of disease, anthropometrics, and cardiovascular disease markers) with 'omic' data (sets of surrogate readouts of the underlying prediabetes and diabetes phenotype), but further study is required ('Discovery'). Better identification of the prediabetes or diabetes phenotype may assist in determining who is most at risk of developing type 2 diabetes mellitus and in whom lifestyle measures and medications are likely to be most effective and safe ('Translation'). Abbreviation: GI, gastrointestinal.

phenotypes include branched-chain and aromatic amino acids [26]. These findings suggest that sets of circulating lipid species and amino acids supplement clinical markers to identify the diverse phenotypes of prediabetes and diabetes, but further study is required (Figure 1).

Individualized Pharmacotherapy in Dysglycemia: Pathophysiology-Directed Prevention and Treatment

Once those most at risk of developing diabetes are identified and their pathophysiology ascertained, it is important to match each individual with a medication that is most likely to be effective, and least likely to cause adverse effects. Knowledge of the metabolic phenotype is likely to permit this, although still unproven. Glucose-lowering modalities target different suites of the pathophysiological impairments underlying dysglycemia (Table 2). The potential benefits of glucose-lowering medication in delaying progression from prediabetes to diabetes and the risk–benefit implications in prediabetes have been comprehensively reviewed elsewhere [27]. Metformin is the oldest and most studied glucose-lowering medication, with documented diversity in glycemic response in randomized clinical studies (Table 1). Given that metformin is the first-line treatment in T2DM and is the recommended therapy for prevention of diabetes if lifestyle recommendations fail, or are not adhered to [6], we limit our discussion to metformin as a case in point. Notably, many of the studies concerning metformin treatment of dysglycemia were performed in patients with T2DM, and the findings may not be generalized to individuals with prediabetes. The liver and the gastrointestinal tract are thought to be the main targets responsible for improvement in glycemia in patients treated with metformin (Table 2). Studies utilizing hyperinsulinemic–euglycemic and hyperglycemic clamps with glucose isotopes suggested that metformin acts to improve liver insulin resistance [28]. Insulin-mediated tissue glucose disposal, predominantly by muscle, was not affected directly by metformin [29]. These

Table 2. Pathophysiological Targets of Glucose-Lowering Medication and Lifestyle Interventions[a,b]

Intervention	Pathophysiological Target[a]	Refs
Metformin	↓ Liver insulin resistance ↔ Muscle insulin resistance ↔ β cell function ↓ Gut microbial dysbiosis ↓ Body weight ↓ Appetite	[27–29,31]
Glucagon-like peptide 1 receptor agonists	↓ Liver insulin resistance ↓ Muscle insulin resistance (possibly secondary to weight loss) ↑ β cell function ↓ Body weight ↓ Appetite	[27,52–54]
Dipeptidyl peptidase 4 inhibitors	↔ Liver insulin resistance ↔ Muscle insulin resistance ↑/↔ β cell function ↔ Body weight	[27]
Sodium-glucose co-transporter 2 inhibitors	↑[c] Liver insulin resistance ↓ Muscle insulin resistance ↑ β cell function ↓ Body weight	[55,56]
Thiazolidinediones	↓ Liver insulin resistance ↓ Muscle insulin resistance ↑ β cell function ↑ Body weight (fat)	[27]
Caloric restriction leading to ≥5% weight loss	↓ Liver insulin resistance ↓ Muscle insulin resistance ↑ β cell function ↓ Body weight ↑ Appetite	[13,57]

[a]Findings from clinical studies in individuals with prediabetes or T2DM.
[b]Thick and thin arrows indicate the degree of the effect being substantial or mild, respectively; ↔, no change.
[c]While endogenous glucose production was enhanced with dapagliflozin, FPG decreased markedly [56].

findings imply that metformin is more likely to be effective in individuals who exhibit, and reverse, liver insulin resistance, but will have to be tested directly in cohorts of individuals with varying degrees of insulin resistance in liver and muscle. An interesting novel concept suggests that the glycemic effect of metformin depends on manipulation of the gastrointestinal tract microbiota (Table 2). An increasing body of evidence suggests that the gut microbiota has an important role in obesity, prediabetes, and diabetes, and alterations in gut microbial composition, termed 'dysbiosis', have been described in T2DM and prediabetes (Table 3). Interestingly, patients with metformin-treated diabetes have a 'healthier' gut microbial composition compared with treatment-naïve patients with diabetes [30], and changes in gut microbial composition with metformin are suggested to mediate the glycemic benefit of the medication [31,32]. It would be interesting to test whether a poor glycemic response to metformin corresponds with the presence of 'metformin-resistant' gastrointestinal microbial communities.

Genetic Variability in Glycemic Response to Metformin

In participants of GoDARTS, heritability explained 23–34% of the variation in the glycemic response to metformin, depending on the glycemic endpoint (absolute, proportional, or adjusted reduction in HbA_{1c}, or achievement of HbA_{1c} target) [33,34]. Metformin is hydrophilic and requires organic cation transporters (OCT) in enterocytes to pass from the intestinal lumen

Table 3. Documented Gut Microbial Composition Differences in Patients with either T2DM or Prediabetes versus Healthy Controls

Condition	Documented Features of Microbial Dysbiosis	Implications	Refs
Prediabetes and T2DM	Enrichment of bacterial species associated with increased capacity for biosynthesis and transport of branched-chain amino acids, including *Prevotella copri* and *Bacteroides vulgatus*	Gut microbiota may partly contribute to increased circulating branched-chain amino acids documented in insulin resistance and T2DM, and may supplement clinical and other indicators of diabetes risk	[50]
	Depletion of butyrate[a]-producing bacteria *Akkermansia muciniphilia*, *Faecalibacterium prausnitzii, Eubacterium rectale, and Eubacterium eligens;* the genera *Faecalibacterium* and *Roseburia*; the phylum *Firmicutes* and class *Clostridia*, as well as depletion of the class *Verrucomicrobiae,* and *Bacteroides* and *Bifidobacterium* genera	Depletion in butyrate-producing bacteria may be used as potential early markers of prediabetes and T2DM Butyrate-producing bacteria are likely to have a protective role against insulin resistance and T2DM	[58–63]
T2DM	Enrichment of opportunistic pathogens associated with infections in organs outside of gastrointestinal tract, including *Bacteroides caccae*, *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, *Eggerthella lenta*, and *Escherichia coli*	Opportunistic pathogens may be responsible for increased oxidative stress activity in gastrointestinal tract and may increase susceptibility to other diseases in patients with T2DM	[59]

[a]Butyrate is a short-chain fatty acid.

to the blood and into the hepatocytes [34]. Coding missense variants in genes encoding OCT1 are purported to explain metformin treatment failure. However, studies in patients with coding missense variants of the *OCT1* gene were inconclusive [35–38]. Interestingly, however, **metformin intolerance** was more likely to occur in patients with T2DM and an increasing number of reduced-function OCT1 alleles in the GoDARTS [39]. Large cohort **genome-wide association studies** (GWAS**)** highlighted gene variants associated with a favorable glycemic response to metformin treatment. Specifically, common variants near the ataxia telangiectasia mutated (*ATM*) gene were associated with a better glycemic response in the GoDARTS [40], and in a meta-analysis including three cohorts of patients with T2DM [41]. However, unexpectedly, the same gene variant was not associated with a more effective prevention of diabetes in the DPP [42]. A gene variant in the gene encoding the hepatic glucose transporter (GLUT)2 has additionally been described and associated with a favorable glycemic response to metformin in a meta-analysis in the Metformin Genetics (MetGen) Consortium, but again, there was no effect of this gene variant on prevention of diabetes [34,43]. In summary, it is likely that glycemic response to metformin and metformin intolerance could be predicted, at least in part, by the individual's genotype, but further studies on larger cohorts, including participants from diverse ethnicities and individuals with prediabetes, are required before genotype-guided metformin treatment may be implemented.

Personalized Nutrition in the Treatment of Dysglycemia

Studies using **nutrigenetics** have emerged over the past decade [44–47]. In addition to a standard weight loss diet, Arkadianos and colleagues provided personalized recommendations tailored to polymorphisms in 19 genes involved in metabolism and inflammation to a small cohort ($N = 93$) of individuals with a history of unsuccessful weight loss attempts [46]. The authors reported that weight loss was similar in the nutrigenetic-tailored and the standard diet groups for up to 300 days, but maintaining the reduced weight long term was significantly enhanced in the nutrigenetic-guided intervention. Reassuringly, in a subcohort of individuals with prediabetes, FPG was more effectively reduced in the nutrigenetic-guided diet group [46]. By contrast, no effect on weight loss magnitude or insulin secretion was reported recently in a relatively large cohort of overweight and obese individuals ($N = 609$) with variants in three genes relevant to fat and carbohydrate metabolism, randomized to low-fat or low-carbohydrate weight loss diets [47]. While these studies led to somewhat disappointing outcomes,

nutrigenetic-guided interventions on substantially larger cohorts with long-term follow-up in patients with prediabetes and those with diabetes are necessary to fully elucidate their potential effect on health outcomes.

Gut microbial dysbiosis is thought to explain many of the comorbidities of obesity (Table 3). While there has been a lack of consensus concerning the specific alterations in the human gastrointestinal microbial composition in metabolic disease, the composition of the human gastrointestinal microbiota is fairly stable over many years and, notably, changes in BMI explained a large proportion of the variation in the stability of fecal microbiota strains [48]. Circulating metabolites, including amino acids, short-chain fatty acids (SCFA), and vitamins originating from the microbial community inhabiting the gastrointestinal tract, serve as active messengers, and may have a profound effect on the immune system [49] and on insulin sensitivity [50]. These may serve as readouts of gut microbial makeup, but further study is required. In support of a gut microbiota-guided intervention, a personalized diet guided by machine-learning algorithms developed to predict low postprandial glycemic response to meals based on the individual's phenotype (e.g., anthropometrics, HbA_{1c}, and serum lipids), diet, physical activity habits, and gut microbial features, improved postprandial glycemia within a single week in subjects with prediabetes [45]. The rapid advancement in gut microbial-sequencing techniques and machine learning in recent years paves the way for personalized interventions in prediabetes and diabetes; however, longer term studies with glycemic control and diabetes prevention endpoints are required.

Outstanding Questions

Which peripheral metabolites will aid in identifying the diverse phenotypes of prediabetes and diabetes?

Is resolving gut dysbiosis a prerequisite to a better glycemic response to metformin in prediabetes and diabetes?

Is personalized medicine possible in patients with prediabetes and those with diabetes?

Concluding Remarks and Future Perspectives

Prediabetes is a heterogeneous condition, with diverse phenotypes, genotypes, and gut microbial characteristics described. Advanced 'omic' technologies may offer viable readouts of the diversity of prediabetes and diabetes in well-designed studies (Figure 1). Recent successful attempts to improve glycemia by personalizing nutrition based on algorithms incorporating the individual's phenotypic and gut microbial features are encouraging. Future research should focus on revealing the role of gut microbial alterations in successful glycemic response to metformin, on revealing the genomic, gut microbiomic, and serum metabolite signatures of the diverse phenotypes of prediabetes and diabetes, and on predictors of glycemic response to insulin-sensitizing modalities in large cohorts of individuals at risk of developing T2DM (see Outstanding Questions).

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References

1. Stefan, N. *et al.* (2016) Phenotypes of prediabetes and stratification of cardiometabolic risk. *Lancet Diabetes Endocrinol.* 4, 789–798
2. Menke, A. *et al.* (2015) Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 314, 1021–1029
3. Wang, L. *et al.* (2017) Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. *JAMA* 317, 2515–2523
4. Knowler, W.C. *et al.* (2009) 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 374, 1677–1686
5. Anjana, R.M. *et al.* (2015) Incidence of diabetes and prediabetes and predictors of progression among Asian Indians: 10-year follow-up of the Chennai Urban Rural Epidemiology Study (CURES). *Diabetes Care* 38, 1441–1448
6. American Diabetes Association (2018) Standards of medical care in diabetes–2018. *Diabetes Care* 41 (Suppl. 1),
7. Leibel, R.L. *et al.* (2015) Biologic responses to weight loss and weight regain: report from an American Diabetes Association Research Symposium. *Diabetes* 64, 2299–2309
8. Rena, G. *et al.* (2017) The mechanisms of action of metformin. *Diabetologia* 60, 1577–1585
9. Sanchez-Rangel, E. and Inzucchi, S.E. (2017) Metformin: clinical use in type 2 diabetes. *Diabetologia* 60, 1586–1593
10. Kahn, S.E. *et al.* (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* 355, 2427–2443
11. Pearson, E.R. *et al.* (2007) Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. *Diabetes* 56, 2178–2182

12. Herman, W.H. *et al.* (2017) Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation. *Diabetes Care* 40, 1668–1677
13. Magkos, F. *et al.* (2016) Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab.* 23, 591–601
14. The Look AHEAD Research Group (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.* 369, 145–154
15. Knowler, W.C. *et al.* (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346, 393–403
16. Tuomilehto, J. *et al.* (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344, 1343–1350
17. Stefan, N. *et al.* (2015) A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. *Diabetologia* 58, 2877–2884
18. Aroda, V.R. *et al.* (2017) Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. *Diabetologia* 60, 1601–1611
19. Haring, H.U. (2016) Novel phenotypes of prediabetes? *Diabetologia* 59, 1806–1818
20. Kahn, S.E. *et al.* (2006) Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 444, 840–846
21. Færch, K. *et al.* (2013) Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: a post-hoc analysis of the longitudinal Whitehall II cohort study. *Lancet Diabetes Endocrinol.* 1, 43–51
22. Chen, D.L. *et al.* (2015) Phenotypic characterization of insulin-resistant and insulin-sensitive obesity. *J. Clin. Endocrinol. Metab.* 100, 4082–4091
23. Abdul-Ghani, M.A. *et al.* (2008) Strong association between insulin resistance in liver and skeletal muscle in non-diabetic subjects. *Diabet. Med.* 25, 1289–1294
24. Tonks, K.T. *et al.* (2016) Skeletal muscle and plasma lipidomic signatures of insulin resistance and overweight/obesity in humans. *Obesity (Silver Spring)* 24, 908–916
25. Lehmann, R. *et al.* (2013) Circulating lysophosphatidylcholines are markers of a metabolically benign nonalcoholic fatty liver. *Diabetes Care* 36, 2331–2338
26. Bogl, L.H. *et al.* (2016) Abdominal obesity and circulating metabolites: A twin study approach. *Metabolism* 65, 111–121
27. Daniele, G. *et al.* (2014) What are the pharmacotherapy options for treating prediabetes? *Expert Opin. Pharmacother.* 15, 2003–2018
28. Edgerton, D.S. *et al.* (2009) Current strategies for the inhibition of hepatic glucose production in type 2 diabetes. *Front. Biosci. (Landmark Ed)* 14, 1169–1181
29. Natali, A. and Ferrannini, E. (2006) Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia* 49, 434–441
30. Forslund, K. *et al.* (2015) Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 528, 262–266
31. Wu, H. *et al.* (2017) Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat. Med.* 23, 850–858
32. Bauer, P.V. *et al.* (2018) Metformin alters upper small intestinal microbiota that impact a glucose-SGLT1-sensing glucoregulatory pathway. *Cell Metab.* 27, 101-117.e5
33. Zhou, K. *et al.* (2014) Heritability of variation in glycaemic response to metformin: a genome-wide complex trait analysis. *Lancet Diabetes Endocrinol.* 2, 481–487
34. Florez, J.C. (2017) The pharmacogenetics of metformin. *Diabetologia* 60, 1648–1655
35. Shu, Y. *et al.* (2007) Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J. Clin. Invest.* 117, 1422–1431
36. Zhou, K. *et al.* (2009) Reduced-function SLC22A1 polymorphisms encoding organic cation transporter 1 and glycemic response to metformin: a GoDARTS study. *Diabetes* 58, 1434–1439
37. Christensen, M.M. *et al.* (2011) The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. *Pharmacogenet. Genomics* 21, 837–850
38. Christensen, M.M. (2015) The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c: Corrigendum. *Pharmacogenet. Genomics* 25, 48–50
39. Dujic, T. *et al.* (2015) Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study. *Diabetes* 64, 1786–1793
40. Zhou, K. *et al.* (2011) Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. *Nat. Genet.* 43, 117–120
41. van Leeuwen, N. *et al.* (2012) A gene variant near ATM is significantly associated with metformin treatment response in type 2 diabetes: a replication and meta-analysis of five cohorts. *Diabetologia* 55, 1971–1977
42. Florez, J.C. *et al.* (2012) The C allele of ATM rs11212617 does not associate with metformin response in the Diabetes Prevention Program. *Diabetes Care* 35, 1864–1867
43. Zhou, K. *et al.* (2016) Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin. *Nat. Genet.* 48, 1055–1059
44. Celis-Morales, C. *et al.* (2017) Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial. *Am. J. Clin. Nutr.* 105, 1204–1213
45. Zeevi, D. *et al.* (2015) Personalized nutrition by prediction of glycemic responses. *Cell* 163, 1079–1094
46. Arkadianos, I. *et al.* (2007) Improved weight management using genetic information to personalize a calorie controlled diet. *Nutr. J.* 6, 29
47. Gardner, C.D. *et al.* (2018) Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The dietfits randomized clinical trial. *JAMA* 319, 667–679
48. Faith, J.J. *et al.* (2013) The long-term stability of the human gut microbiota. *Science* 341, 1237439
49. Levy, M. *et al.* (2016) Metabolites: messengers between the microbiota and the immune system. *Genes Dev.* 30, 1589–1597
50. Pedersen, H.K. *et al.* (2016) Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 535, 376–381
51. Lindstrom, J. *et al.* (2008) Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. *Diabetes Care* 31, 857–862
52. Cervera, A. *et al.* (2008) Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* 294, E846–E852
53. Gastaldelli, A. *et al.* (2016) Exenatide improves both hepatic and adipose tissue insulin resistance: A dynamic positron emission tomography study. *Hepatology* 64, 2028–2037
54. Flint, A. *et al.* (1998) Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J. Clin. Invest.* 101, 515–520
55. Ferrannini, E. *et al.* (2014) Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J. Clin. Invest.* 124, 499–508
56. Merovci, A. *et al.* (2014) Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J. Clin. Invest.* 124, 509–514

57. Sumithran, P. *et al.* (2011) Long-term persistence of hormonal adaptations to weight loss. *N. Engl. J. Med.* 365, 1597–1604

58. Larsen, N. *et al.* (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 5, e9085

59. Qin, J. *et al.* (2012) A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490, 55–60

60. Wu, X. *et al.* (2010) Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Curr. Microbiol.* 61, 69–78

61. Karlsson, F.H. *et al.* (2013) Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 498, 99–103

62. Zhang, X. *et al.* (2013) Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 8, e71108

63. Yassour, M. *et al.* (2016) Sub-clinical detection of gut microbial biomarkers of obesity and type 2 diabetes. *Genome Med.* 8, 17