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Review

A Review of Prediabetes: Diagnosis, Consequences and Interventions

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Abstract: Prediabetes describes a state of dysglycemia that is the "watershed" between normoglycemia and type 2 diabetes. This review will examine the definitions of prediabetes, the adverse complications of prediabetes, the treatment of prediabetes, and diabetes prevention.

Keywords: prediabetes; diabetes; impaired fasting glucose; impaired glucose tolerance

1. Introduction

Health care providers have long recognized that the relationship between blood glucose and cardiovascular disease (CVD) is a continuum, necessitating the need to categorize individuals with a glycemic status just below the cutoff point for diagnosis of diabetes [1]. While the concept of an intermediate state of impaired glucose regulation between normal glucose homeostasis and diabetes is not new, its characterization based on specific diagnostic methods has undergone significant changes in the recent decades.

The most recent and key publications were included in developing this review. Seach terms included "prediabetes" and a variety of pertinent disease-related terms such as "cardiovascular disease", "stroke", "peripheral vascular disease", "renal disease", "kidney disease", etc. We were careful to examine the nature of the control populations used in the various studies as some researchers used only historic controls. This review presents: [I] the consensus of current opinion concerning the definition of prediabetes, [II] the adverse consequences of prediabetes, and [III] the management of prediabetes.

2. Current Definition of Prediabetes

The current American Diabetes Association (ADA) criteria for diagnosing prediabetes are shown in Table 1 [2].

Table 1. Criteria defining prediabetes in nonpregnant individuals, with permission from Ref. [2].

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

2.1. Historical Perspectives

2.1.1. Origin of Impaired Glucose Tolerance

Impaired glucose tolerance (IGT) was the first prediabetes category to be formally recognized [3]. The proposal was endorsed by the ADA, and it was subsequently adopted by the World Health Organization (WHO) in 1980 [4]. IGT replaced old terms which were often confusing, such as "chemical", "borderline", "latent", "subclinical", and "asymptomatic" diabetes. The definition of IGT was based on a two-hour plasma glucose (2HPG) of 140 mg/dL or greater, but less than 200 mg/dL during a 75 g oral glucose tolerance test (OGTT) [3]. Additionally, the fasting plasma glucose (FPG) in the individual must be below the diabetic range (currently fasting hyperglycemia is defined as =>126 mg/dL). Remarkably the post-glucose-load cutoff points at 2 h defining IGT (140–199 mg/dL) have remained the same as when the term "IGT" was first introduced.

2.1.2. Emergence of Impaired Fasting Glucose

The National Diabetes Data Group (NDDG) used distributions of glucose levels in relation to symptomatic diabetes, not correlations between glucose levels and vascular complications, to define the cutoff point for diabetes [3]. About two decades later, an ADA Expert Committee focused primarily on the relationship between glucose levels and the presence of long-term complications [5]. While examining the relationship between FPG and 2HPG values and retinopathy, it was observed that a previous FPG cutoff point of 140 mg/dL was significantly above the glucose level at which the prevalence of retinopathy began to rise, hence the ADA committee recommended that the FPG cutoff point defining hyperglycemia be lowered to 126 mg/dL. The ADA also introduced a new category of prediabetes, impaired fasting glucose (IFG), as a means of classifying individuals with FPG levels between a normal state and diabetes, analogous to IGT as an intermediate metabolic state between normoglycemia and diabetes, but based on their FPG. The initial FPG cutoff points recommended were 110 mg as the lower limit and 125 mg/dL as the upper limit of IFG. Subsequently, in 2003, the range for IFG was changed to 100–125 mg/dL with the aim of capturing populations at a risk similar to that of IGT [6]. Unfortunately, IFG and IGT are not synonymous, each having a unique glycemic profile. While the WHO adopted the new IFG category, it retained the original cutoff point of 110 mg/dL as the lower limit [7]. The WHO still considers the OGTT as the "gold standard" test for the diagnosis of diabetes, but the ADA no longer considers it as such, except the ADA recommended it for screening in some unique situations such as during pregnancy, and in patients with cystic fibrosis; however, without an OGTT, a diagnosis of IGT cannot be made.

2.1.3. Combined IFG and IGT

There is an overlap between IFG and IGT. To enhance the study of the separate characteristics of IFG and IGT, classifications of isolated IFG and isolated IGT that are mutually exclusive have been proposed [8]. Isolated IFG implies a FPG of 100–125 mg/dL with a 2-h PG value of less than 140 mg/dL, whereas isolated IGT is 2-h PG value of 140–199 mg/dL with the fasting PG level below 100 mg/dL. The combined IFG and IGT category fulfills both IFG and IGT criteria. Persons with combined IFG and IGT display nearly twice the rate of developing diabetes compared with those with just one of the two entities [8].

2.1.4. Emergence of Hemoglobin A1C as a Diagnostic Tool for Prediabetes

Hemoglobin A1C (A1c) was not previously considered a reliable screening test for diabetes or prediabetes because of variation in the assays and analytical imprecision. As a result of the standardization of most assays to those used in the Diabetes Control and Complications Trial, and extensive assay and manufacturer certifications of the A1c assays [9,10], A1C was accepted by the ADA in 2010 for use as a screening and diagnostic marker [11]. It has now become a widely used diagnostic tool. The recommendation for the use of A1C criteria in identifying people with prediabetes was based on the NHANES (National Health and Nutrition Examination Survey data) 2005–2006 data. Individuals with A1C values of 5.7% to 6.4% are now categorized as having prediabetes; persons with A1c values of 6.0% to 6.4% are at the highest risk of developing type 2 diabetes according to the report of an International Expert Committee [12]. The prevalence of retinopathy increased beginning at an A1C of 5.7%. Furthermore, A1C was more predictive than FPG in identifying cases of retinopathy.

One advantage of the A1C test is that unlike PG measurements, there is no need for special preparation for blood drawing such as timing, fasting, or the administration of a glucose load, thus making A1c testing more convenient. Moreover, A1C correlates well with average glucose level and the vascular complications of diabetes. There is a continuum of risk for the development of type 2 diabetes based on increasing A1C levels similar to increasing measures of glucose [12].

In conditions associated with an altered relationship between A1C and glycemia, for example, some hemoglobin variants, pregnancy, glucose-6-phosphate dehydrogenase deficiency, hemodialysis, recent blood loss or transfusion, hemolysis, or erythropoietin therapy, the ADA recommends the use of PG criteria for diagnostic purposes [2].

2.1.5. Heterogeneity of Prediabetes

Both IFG and IGT display heterogeneous pathogeneses, and this may partly account for the different rates of progression to type 2 diabetes and risk of CVD in affected individuals. The heterogeneity of IGT was classically illustrated by Stern et al. four decades ago [13]. According to their hypothesis, the IGT category consists of at least three entities which, although conceptually distinct, could not be distinguished by glucose tolerance testing alone. Their arguments rest heavily on the concept that plasma glucose concentrations are bimodally distributed in populations (Figure 1), exemplified by the Pima Indians and Pacific Islanders [14,15]. The first group in the IGT category, which they tagged as "IGT normal," belong to the upper end of the normal (Gaussian) distribution, implying that their glucose tolerance happens to fall in the upper portion of the normal range. The second group consists of individuals who truly have diabetes but have "false-negative" glucose tolerance values because their glucose tolerance values do not exceed the current cutoff points for diabetes during their OGTT. The third group consists of individuals who are truly in transition from normal to diabetic, referred to as "IGTs in transition." Based on the bimodality also observed in fasting glucose distributions [15], this concept is applicable in explaining the heterogeneity of the IFG category as well. Some experts contend that it is difficult to identify bimodal glucose distributions in other population groups, for instance, among whites [12]. A likely explanation is the lower prevalence of diabetes in those populations, in comparison with the very high-risk populations, such as the Pima Indians and the Nauruans (a group of Pacific Islanders).

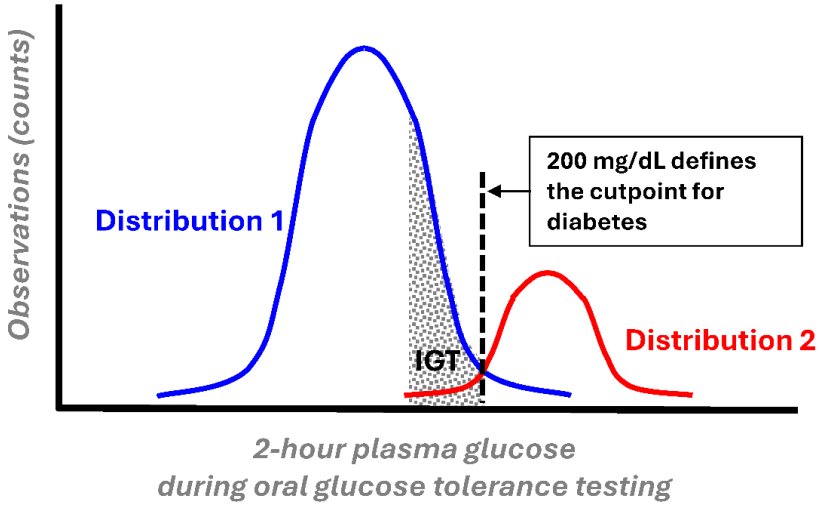

Figure 1. A schematic representation of the hypothetical bimodality of 2-h plasma glucose concentrations during an oral glucose tolerance test (OGTT). Distribution 1 represents the nondiabetic population. Distribution 2 represents the diabetic population. The shaded area represents impaired glucose tolerance (IGT) (e.g., plasma glucose between 140–199 mg/dL) that includes 'IGT normal', 'false negative for diabetes', and 'IGT in transition.'.

2.1.6. Natural History of Prediabetes

The natural history of prediabetes defined by IFG or IGT is variable: 25% revert to normal glucose tolerance, 50% remain in the abnormal glycemic state, but about 25% progressed to diabetes over three to five years [8]. Higher rates of progression to type 2 diabetes have also been reported. The poor intraindividual reproducibility of glucose measurements, especially during the OGTT, are contributory factors to the difficulty in studying the natural history of IFG and IGT [16,17].

The risk factors for progression of prediabetes to type 2 diabetes include increasing age and increasing severity of obesity. These clinical risk factors are in consonance with the underlying metabolic defects, impaired insulin secretion and insulin resistance.

The phenotypic differences in rates of progression are partly a function of diagnostic thresholds, fasting and post glucose load hyperglycemia. However, they represent phenotypes with distinct natural histories in the evolution of type 2 diabetes [18].

Although insulin resistance plays a dominant role, especially in people with obesity, beta cell failure is thought to be central to the development and progression of type 2 diabetes. It precedes and predicts type 2 diabetes onset and progression, is in part genetically determined. Multiple pathways underlie decreased beta cell function and mass, some of which may be shared, and may also be a consequence of processes that initially caused beta cell dysfunction [19]. All these variables explain, at least in part, why there are lean individuals with type 2 diabetes.

Various interventions have been shown to alter the natural history of IFG or IGT progression to type 2 diabetes. All of the controlled clinical trials have measured changes in glycemia as their primary outcome. A natural history definition based on pathophysiologic parameters might be more sensitive to, and discriminate better among the various effects of particular interventions than changes in glycemia [8]. The results of some studies support the beneficial effect of focusing on the underlying pathophysiology, specifically a reduction in insulin resistance and an improvement in relative insulin secretion [20,21]. However, a nonglycemic definition of the natural history of IFG/IGT is complicated, more expensive to measure, and less easily translatable to clinical practice [8].

2.1.7. Pathophysiology of the Metabolic Defects in Prediabetes

Isolated IFG and isolated IGT differ in their site of insulin resistance [8]. Persons with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance [22]. During an OGTT the PG concentration of an individual with isolated IGT remains elevated (by definition 140–199 mg/dL) at 120 min (Figure 2), whereas the FPG in isolated IFG is higher than in NGT (normal glucose tolerance) and isolated IGT, and the PG concentration at 30–60 min are greater than in both NGT and isolated IGT (note: 30 and 60 min time points are not part of a standard OGTT). Subsequently, the plasma glucose concentration in IFG declines to near-baseline levels at 120 min (Figure 2). The distinct OGTT curves reflect different pathophysiologic disturbances in glucose homeostasis in these conditions. The PG curve of a person with combined IFG and IGT manifests the characteristics of both [8]. The pattern of impaired insulin secretion also differs between the two groups. Individuals with isolated IFG manifest a decrease in first-phase insulin secretory response to intravenous glucose and early-phase insulin response to oral glucose. However, late-phase plasma insulin response during OGTT is less severely impaired than in IGT. Persons with IGT have severe defects in both early- and late-phase insulin responses to intravenous and oral glucose [22]. Not surprisingly, individuals with both IFG and IGT manifest both muscle and hepatic insulin resistance [8].

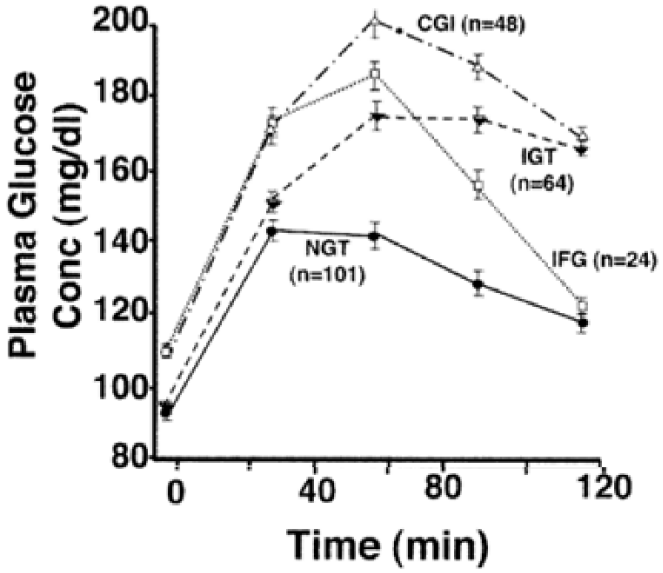

Figure 2. Plasma glucose concentrations during an OGTT performed in subjects with either normal glucose tolerance (NGT), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or combined glucose intolerance (CGI). Adapted with permission from Nathan et al. [8].

One group reported that during euglycemic clamp testing, the suppressibility of basal glucose with insulin was higher in IFG, but not in IFG/IGT, compared with NGT, suggesting that IFG/IGT may be a distinct prediabetic syndrome rather than a progression from IFG. [23]. However, data from other studies [24,25] are in consonance

with those described earlier [22]. We suspect that the heterogenous nature of both IFG and IGT may be a factor in the apparent variation in the pathophysiological disturbances observed in the persons with combined glucose intolerance (IFG and IGT).

The natural progression of dysglycemia involves increasing insulin resistance and loss of pancreatic beta-cell function. Also, aberrant expression of proinflammatory cytokines is thought to play some role in the progression from prediabetes to type 2 diabetes and the related vascular complications [26].

3. Prediabetes—Macrovascular, Microvascular and Neuropathic Diseases

In this section, we examine the question: "Does prediabetes increase a person's risk for macrovascular, microvascular or neuropathic complications compared to normoglycemic individuals?" To address this question, Pubmed was searched using key terms reflective of prediabetes crossed with relevant terms such as macrovascular disease, cardiovascular disease (CVD), cerebrovascular disease, peripheral vascular disease (PVD), microvascular disease, retinopathy, nephropathy, and neuropathy.

3.1. Cardiovascular Disease

CVD, in its broadest sense, refers to any large- or medium-sized arterial vascular disease, usually caused by atherosclerosis [e.g., atherosclerotic CVD (ASCVD)], that manifests as disease of the heart, central nervous system (CNS), or peripheral vasculature. Heart disease usually involves the coronary arteries but can also affect smaller vessels. Cerebrovascular disease can manifest as stroke, transient ischemic attack (TIA) or chronic cerebral ischemia. Peripheral vascular disease can affect the renal arteries or arteries of the lower extremities. CVD can affect the aorta and its branches.

Overall, persons with prediabetes are at increased risk for all forms of ASCVD and often increased mortality is demonstrated [27]. Risk of cardiovascular mortality appears to double in persons with prediabetes compared to normoglycemic individuals [26]. A meta-regression analysis found that cardiovascular event risk increased 1.33-fold in individuals with a FPG of 110 mg/dL and a 2-h PG of 140 mg/dL on oral glucose tolerance testing (both measures fall within the prediabetes spectrum) compared with individuals with a normal FPG (75 mg/dL) [27]. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study reported that cardiovascular mortality and FPG were positively correlated [28]. Some researchers, however, have found that the magnitude to which prediabetes increases the risk of cardiovascular disease may be modest, and not all studies show that prediabetes definitely increases the risk of CVD [29]. Nevertheless, the preponderance of the data is that prediabetes is associated with increased risk for CVD [30].

IFG and IGT may not equally predict increased CV mortality with IGT being a stronger predictor of mortality than IFG [31]. This emphasizes an important concept: all measures of prediabetes (e.g., IFG, IGT, IFG together with IGT, and an A1c of 5.7% to 6.4%) may not all have an equal effect on increasing the likelihood of adverse events in the prediabetic state. Several publications report that IGT and A1c correlate more with CVD risk than IFG [32,33].

The frequency of prediabetes in persons with coronary artery disease ranges between ~20% and ~35% [34]]. In cases of chronic heart failure, ~40% of patients have prediabetes. In persons with prediabetes or diagnosed diabetes, every increase in A1c of 1% increases the risk for a cardiovascular event by 25% [34].

Among persons surviving a myocardial infarction (MI) who previously were not diagnosed with diabetes, 40% had prediabetes 3 months following their MI [35]. Overall, the magnitude of CVD risk in persons with prediabetes appears to be increased by 10% to 40% compared to normoglycemic individuals [36,37].

3.2. Cerebrovascular Disease

Prediabetes is a risk factor for cerebrovascular disease [38]. This should not be surprising because atherosclerosis is a systemic disease [39]. After 4.5 years of observation, the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated an ~9% increase in stroke, MI, or cardiovascular death for every increase in FPG of ~20 mg/dL. For an increase in A1c of 1%, there was a relative risk of 1.07 for an adverse cardiovascular outcome including cerebrovascular disease [40]. Of persons with ischemic stroke or TIA, between 32% and 34% have prediabetes [34].

3.3. Peripheral Vascular Disease

Persons with prediabetes are at increased risk for PVD among other adverse CV outcomes [41]. Among people with PVD, between 26% and 28% are diagnosed with prediabetes [34].

3.4. Retinopathy

Diabetic retinopathy is a leading cause of blindness worldwide. Initially, affected individuals can be asymptomatic, followed later by the recognition of floaters, distorted or blurred vision, progressive loss of visual acuity, vitreous hemorrhage, and, all too frequently, blindness [42]. Unfortunately, microvascular disease often precedes the diagnosis of type 2 diabetes and can be detected in persons with prediabetes [43]. Retinopathy is increased in frequency by more than 100% in prediabetes compared to a normal glucose-tolerant population (6.7% versus 3.0%) [44]. Similar findings were summarized by Kirthi et al. [45].

3.5. Neuropathy

Diabetic neuropathy can affect sensory nerves, motor nerves or the autonomic nervous system [46]. Sensory defects can accentuate or impair perception and can be distributed in a focal or diffuse pattern. The most typical distal extremity neuroparthy is that of a glove and-stocking distribution. The onset of sensory neuropathy is usually subtle. Motor neuropathy can present together with sensory neuropathy (sensorimotor neuropathy). Autonomic neuropathies can affect the sweat glands, heart and vasculature, the gut, and the genitourinary tract.

The microvascular complications of prediabetes and diabetes most strongly relate to chronic hyperglycemia [47]. Similar to retinopathy, neuropathy can be observed in persons with prediabetes [48,49]. Papanas et al. report that ~25% to 60% of persons with idiopathic peripheral neuropathy are prediabetic [50]. From the vantage point of persons diagnosed with prediabetes, ~10% to ~25% display peripheral neuropathy, and neuropathic pain is approximately equally common. Conceptually, as glycemia increases from normoglycemic to prediabetes and then to type 2 diabetes, the frequency of neuropathy rises. However, some controversy exists as to whether the risk of neuropathy is increased in prediabetes [51].

Autonomic neuropathy has been recognized in persons with prediabetes. Cardiovascular autonomic neuropathy (CAN) has specifically been studied [52,53]. CAN progressively increased in frequency from 4.5% in normoglycemic individuals, to 5.9% in persons with IGT, to 8.1% in persons with IFG, and then to 11.4% in persons with combined IGT and IGT [54].

3.6. Nephropathy

The clinically evident findings of diabetic nephropathy (DN) range from persistent increased excretion of albumin (stage 3 DN) to frank end-stage renal disease requiring dialysis or kidney transplantation (stage 5 DN) [55]. Diabetes also predisposes to diabetic renovascular disease (renal artery atherosclerosis), urinary tract infections, papillary necrosis, nephrotic syndrome, and neurogenic bladder, as well as, being associated with obesity-related glomerulopathy (ORG; via the metabolic syndrome). From many studies, prediabetes is associated with chronic kidney disease together with many other adverse outcomes [56]. Unfortunately, like other forms of microvascular disease, persons with prediabetes can be affected by DN [57].

4. Diabetes Prevention and Reduction of Long-Term Complications

In this section, we examine whether diabetes prevention leads to a reduction in long-term vascular complications.

4.1. Diabetes Prevention and Reduction of Long-Term Vascular Complications

The ongoing global epidemic increase in type 2 diabetes and prediabetes necessitates the need to prevent or delay the development of diabetes, and the associated vascular complications. Management of prediabetes has gained considerable attention since lifestyle and pharmacologic interventions potentially provide the opportunity to mitigate the risk of developing type 2 diabetes.

The relationship between diabetes prevention and the reduction of long-term complications is still unclear. CVD is of multifactorial origin; it is not diabetes specific. Theoretically, prevention of diabetes could still mitigate the risk of CVD. The effect of diabetes prevention on the reduction of microvascular disease is expected to be stronger since hyperglycemia has a greater impact on microvascular than macrovascular disease.

Diabetes prevention studies that report its effects on long-term complications are limited in number and difficult to interpret [58]. Furthermore, prediabetes is associated with increased risk of clinical outcomes even without progression to diabetes. Progression to diabetes may explain less than one quarter of the risks of clinical outcomes associated with prediabetes [59,60].

There are several studies of small sample size or short duration that have examined the role of lifestyle intervention and/or pharmacotherapy in diabetes prevention that also report vascular outcomes. Some studies, not

specifically designed as diabetes prevention trials, have also reported on diabetes prevention, and the vascular complications as secondary outcomes [58]. This review will focus on the major studies.

4.2. Microvascular Disease

Several studies across different populations have shown the effectiveness of lifestyle and pharmacologic intervention in preventing progression to type 2 diabetes and the subsequent development of CVD. Nevertheless, only a few studies reported the association of diabetes prevention with microvascular or CVD complications [58]. This is because most of the diabetes prevention trials were of insufficient duration to allow such an evaluation. Also, most of the studies were designed to evaluate metabolic outcomes, not microvascular or cardiovascular outcomes. Available limited long-term data are largely from the Da Qing Diabetes Prevention Study (DQDPS) [61], and the Diabetes Prevention Program (DPP) [62], and their respective outcome follow-up studies (DQDPOS and DPPOS) [63–65]. Both prevention studies utilized lifestyle interventions aimed at ameliorating obesity and sedentary lifestyle which are major risk factors for diabetes. Additionally, pharmacotherapy with metformin was employed by the DPP in an arm of the study.

In the DQDPS, 577 subjects diagnosed with IGT based on the WHO criteria during screening for IGT and diabetes among 110,660 Chinese adults were followed over a 6-year period to identify who would develop type 2 diabetes. Participants were randomized in the clinical trial either to a control group, or to one of three active treatment groups: [i] diet only, [ii] exercise only, or [iii] diet plus exercise. In a proportional hazards analysis adjusted for differences in baseline body mass index (BMI) and FPG, the diet, exercise, and diet-plus-exercise interventions were associated with 31% ($p < 0.03$), 46% ($p < 0.0005$), and 42% ($p < 0.005$) reductions in risk of developing diabetes, respectively [61].

Since the reduction in diabetes incidence was considered not significantly different among the three original randomized lifestyle intervention groups at the end of the trial, the three intervention groups were combined into a single group to improve study power in the follow-up analysis of complications. The outcome study DQDPOS, which entailed follow-up for 20–30 years, reported long-term effects of lifestyle interventions on macrovascular and microvascular complications, and mortality [63,64].

The subjects in the combined lifestyle intervention groups had a 51% lower incidence of diabetes than the controls (hazard rate ratio [HRR] 0.49; 95% CI 0.33−0.73) during the active intervention period, and a 43% lower incidence (0.57; 0.41−0.81) over the 20-year period. Participants in the intervention group had an average of 3.6 fewer years of being diagnosed with diabetes. During their 30-year follow-up, the subjects in the combined intervention group had a median delay in diabetes onset of 3.96 years (95% CI 1.25 - 6.67; $p = 0.0042$), and a lower incidence of microvascular complications (0.65, 0.45–0.95; $p = 0.025$). The incidence of retinopathy was 40% lower (95% CI 5–62, $p = 0.032$) in the intervention group than in the control group; incidences of nephropathy and neuropathy were also numerically lower, but not statistically significantly reduced [64].

In the DPP, 3234 nondiabetic adults (68% women, and 45% from minority groups) with elevated fasting and post-load PG concentrations were randomly assigned to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of achieving at least a 7% weight loss and at least 150 min of physical activity per week. The participants were followed for an average of 2.8 years (range, 1.8 to 4.6). The incidences of diabetes were 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence of progression to diabetes by 58% (95% CI 48–66%) and metformin reduced the incidence of progression to diabetes by 31% (95% CI 17–43%), as compared with placebo. Lifestyle intervention was significantly more effective than metformin [62].

During a mean follow-up of 15 years, diabetes incidence was reduced by 27% in the lifestyle intervention group (hazard ratio 0.73, 95% CI 0.65–0.83; $p < 0{\cdot}0001$) and by 18% in the metformin group (0.82, 0.72–0.93; $p = 0{\cdot}001$), compared with the placebo group, with declining between-group differences over time. The prevalences at the end of the study for the aggregate microvascular outcomes were not significantly different between the treatment groups in the total cohort (placebo 12.4%, 95% CI 11.1–13.8%; metformin 13.0%, 11.7–14.5%; lifestyle intervention 11.3%, 10.1–12.7%). However, in women (n = 1887) the lifestyle intervention was associated with a lower prevalence of diabetes (8.7%, 95% CI 7.4–10.2%) than in the placebo (11.0%, 9.6–12.6%) and metformin (11.2%, 9.7–12.9%) groups, with reductions in the lifestyle intervention group of 21% ($p = 0.03$) compared with placebo and 22% compared with metformin ($p = 0.02$). Compared with participants who developed diabetes, those who did not develop diabetes had a 28% lower prevalence of microvascular complications (relative risk 0.72, 95% CI 0.63–0.83; $p < 0.0001$) [65].

The data from both major studies, Da Qing (DQDPS/DQDPOS) and DPP (DPP/DPPOS), suggest a reduction in microvascular complications and amelioration of CVD risk factors with interventions to prevent or reduce the likelihood of developing type 2 diabetes.

4.3. Macrovascular Disease

Macrovascular disease plays a major role in the morbidity and mortality associated with diabetes, hence the significance of including the risk factors, CVD events, and mortality and other measures of CVD in intervention trials. Similarly, as with microvascular complications, the effects of diabetes prevention on CVD outcomes may be confounded by the extra glycemic effects of the intervention used in the individual trials [58].

Apart from DQDPOS, the only other study that has demonstrated a reduction in CVD events was the multinational Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) [66]. Only DQDPOS has shown a decrease in CVD and overall mortality.

In the 20-year follow-up study of the DQDPS, there was no significant difference between the intervention and the control groups in the rate of first CVD events (HRR 0.98; 95% CI 0.71−1.37), CVD mortality (0.83; 0.48−1.40), and all-cause mortality (0.96; 0.65−1.41) [63]. However, the study was not adequately powered to detect those differences.

In the 30-year follow-up of DQDPOS, the subjects in the combined intervention group had fewer cardiovascular disease events (hazard ratio 0.74, 95% CI 0.59–0.92; $p = 0.006$), compared with the controls, fewer cardiovascular disease deaths (0.67, 0.48–0.94; $p = 0.022$), lower all-cause mortality (0.74, 0.61–0.89; $p = 0.0015$), and an average increase in life expectancy of 1.44 years (95% CI 0.20–2.68; $p = 0.023$) [64].

In the STOP-NIDDM trial involving 1428 subjects with IGT, acarbose treatment was associated with a 49% relative risk reduction in the development of cardiovascular events (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.28–0.95; $p = 0.03$) and a 2.5% absolute risk reduction. Among cardiovascular events, the major reduction was in the risk of MI (HR, 0.09; 95% CI, 0.01–0.72; $p = 0.02$). Acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension (HR, 0.66; 95% CI, 0.49–0.89; $p = 0.006$) and a 5.3% absolute risk reduction. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24–0.90; $p = 0.02$) and hypertension (HR, 0.62; 95% CI, 0.45–0.86; $p = 0.004$) associated with acarbose treatment was still statistically significant [66].

4.4. Intervention Approach: Lifestyle Intervention and/or Pharmacotherapy for Diabetes Prevention?

4.4.1. Early Intervention

Despite the inadequacy of direct data regarding the benefits of type 2 diabetes prevention on long-term complications, the ADA emphasized the need for an early intervention with the goal of delaying the onset of type 2 diabetes, thus postponing the requirement for treatment [8]. The concept is based on the prospect of preserving beta-cell function, likely delaying or preventing microvascular complications, and possibly macrovascular disease.

4.4.2. Lifestyle Intervention

The DPP [62] and the FDPS (Finnish Diabetes Prevention Study) [67] and several other studies clearly demonstrated the efficacy of lifestyle modification therapy for diabetes prevention; both studies showed a risk reduction of 58%.

A major focus is targeting obesity and maintaining a healthy weight. The lifestyle modification approach emphasizes modest weight loss (5–10% of body weight) and moderate-intensity physical activity (30 min daily or 150 min per week) for individuals with prediabetes. While acknowledging that the population enrolled in the clinical trials might not exactly reflect the general population, the ADA still concluded that lifestyle modification would benefit all people with IFG, IGT or an A1c in the prediabetic diabetic range [8,68].

The nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total fat and calories [69]. Available evidence indicates that there is no specific ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes [70]. Therefore, the ADA recommends that macronutrient distribution be based on an individualized assessment of current eating patterns, preferences, and metabolic goals [68]. Based on the results of other trials, a variety of eating patterns, including Mediterranean-style and low-carbohydrate eating plans, are also considered appropriate for individuals with prediabetes [70,71].

4.4.3. Pharmacotherapy

The Food and Drug Administration has not approved any drugs for type 2 diabetes prevention. Metformin has the most safety data as a pharmacologic therapy for diabetes prevention [65,68]. Metformin was less effective than lifestyle modification in the DPP, but group differences diminished over time in the DPPOS. According to ADA, metformin therapy should be considered in adults with prediabetes aged 25 to 59 years with a BMI greater than or equal to 35 kg/m^2, those with higher A1c (specifically 6.0–6.4%), individuals with higher FPG (110 mg/dL or greater), or a history of gestational diabetes mellitus [68].

Other individuals with prediabetes for whom metformin therapy can be considered are those with other risk factors associated with type 2 diabetes such as a family history of affected first-degree relatives, elevated triglycerides, low HDL cholesterol, and hypertension [8].

Cost and safety profiles particularly favor the use of metformin for the prevention of type 2 diabetes. Acarbose, employed in the STOP-NIDDM trial, seems to be as effective as metformin, but it is poorly tolerated because of gastrointestinal adverse effects, and it is more expensive than metformin.

In the XENDOS (XENical in the prevention of diabetes in obese subjects) study, granted that it was not designed as a diabetes prevention trial, when compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes over 4 years; the hazard ratio (0.627 [95% CI 0.455–0.863]) corresponds to a 37.3% decrease in the risk of developing diabetes with orlistat compared with placebo [72]. Orlistat is currently available over the counter, making it affordable. However, like acarbose, orlistat is poorly tolerated due to gastrointestinal side effects.

In the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial, rosiglitazone reduced the risk of type 2 diabetes in individuals with IGT by 62% after approximately 3 years. However, it significantly increased the incidence of heart failure, compared with placebo (0.5 vs. 0.1%, p= 0.01). Other cardiovascular event rates were much the same in both groups [73]. In the ACT NOW trial (Actos Now for the prevention of diabetes), pioglitazone, another thiazolidinedione (TZD), reduced the prevalence of type 2 diabetes by 72% [74]. The protective effect of pioglitazone on incidence of diabetes was attenuated after discontinuation of the therapy [75].

In the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study, which involved 12,537 individuals with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes, insulin glargine was used to target normal fasting plasma glucose levels for a median of 6.2 years. It had a neutral effect on cardiovascular outcomes. Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight [76].

With the rising rates of obesity accompanied by prediabetes, glucagon-like peptide-1 (GLP-1) receptor agonists (GLPRAs) and a dual glucose-dependent insulinotropic polypeptide (GIP)/ GLP-1 receptor agonist are being increasingly used, despite cost and their primary usage as injectables. The frequent use of these drugs is not surprising because they are the most potent weight loss drugs that are currently available [77]. GLP-1 receptor agonists also improve insulin sensitivity secondary to weight loss. In preclinical models, tirzepatide, a dual agonist, is associated with weight-independent insulin sensitization [78].

In STEP 10 (Research Study Looking at How Well Semaglutide Works in People Living with Obesity and Prediabetes), a randomized, double-blind, placebo-controlled, multicenter phase 3 trial, 81% of participants with obesity and prediabetes reverted to normoglycemia at week 52 with semaglutide 2.4 mg compared with placebo 14% (odds ratio 19.8 [95% CI 8.7–45.2]; $p < 0{\cdot}0001$). Adverse events leading to treatment discontinuation occurred in 6% participants in the semaglutide 2.4 mg group versus 1% in the placebo group [79].

Tirzepatide was used in the SURMOUNT-1 (A Study of Tirzepatide (LY3298176) in Participants with Obesity or Overweight) trial. At 176 weeks, fewer participants received a diagnosis of type 2 diabetes in the tirzepatide groups than in the placebo group (1.3% vs. 13.3%; hazard ratio, 0.07; 95% CI 0.0–0.1; $p < 0.001$). After 17 weeks off treatment or placebo, 2.4% of the participants who received tirzepatide and 13.7% of those who received placebo had type 2 diabetes (hazard ratio, 0.12; 95% CI, 0.1–0.2; $p < 0.001$). There were mild to moderate gastrointestinal adverse events, most of which occurred primarily during the dose-escalation period in the first 20 weeks of the trial [80].

All the medications tested for type 2 diabetes prevention had some adverse effects, and in some cases the side effects were severe. Drug discontinuation often resulted in glycemic rebound [26,75,81–83]. Given the limitations of pharmacotherapy, the ADA recommended lifestyle management as the first line approach for type 2 diabetes prevention and consideration of metformin therapy in high-risk individuals, as highlighted above. Periodic assessment of vitamin B12 level in those taking metformin chronically is recommended to evaluate for possible deficiency, especially in individuals on a higher dose of metformin of 1500 mg/day or greater [68].

In the most recent ADA guidelines, there is a recommendation that people with a history of stroke and evidence of insulin resistance and prediabetes may be considered for pioglitazone therapy to lower their risk of stroke or MI. It is noted that the benefit still needs to be balanced with the increased risk of weight gain, edema, and fractures [68]. Lower doses of the TZD may mitigate the risk of adverse effects but may also be less efficacious.

Based on the current understanding of the underlying pathophysiological abnormalities which characterize IGT and IFG, some researchers indicate that we now have more insights on appropriate pharmacological interventions that can slow or halt their progression to type 2 diabetes [22]. The concept is that individuals with IFG, who manifest predominant liver insulin resistance, are most likely to benefit from agents (for instance, metformin) that reduce hepatic insulin resistance, as was demonstrated in the DPP [62], while those with IGT, who predominantly have muscle insulin resistance plus severely impaired insulin secretion, are more likely to respond to agents that improve skeletal muscle insulin resistance, such as peroxisome proliferator–activated receptor- agonists, the TZDs [20], in combination with an insulin secretagogue, such as a GLP-1 analog. A GLP-1 receptor agonist can improve insulin resistance in skeletal muscle by enhancing GLUT4 expression, an insulin-responsive glucose transporter, thus improving insulin signaling pathways in muscle cells. Also, a GLP-1 agonist can enhance muscle microvascular perfusion, leading to better insulin delivery to muscle tissue [84,85]. The clinical impact is yet to be determined.

Regarding which is a more effective approach to prevent or delay type 2 diabetes onset, lifestyle intervention or pharmacological therapy, the overwhelming evidence is clearly in favor of the former: lifestyle intervention. An intensive lifestyle intervention, while associated with very significant reduction in the risk of progression of prediabetes to type 2 diabetes, may also potentially produce a modest reduction in CVD risk factors, with virtually no serious adverse effects.

5. Discussion

There is no single definition of prediabetes [86,87]. However, there is also a lack of consensus in defining the metabolic syndrome and hypertension [88,89]. There is much more singularity as to the definition of diabetes mellitus [2].

Prediabetes can be considered a “way station” on the road between normoglycemia and type 2 diabetes. Additionally, prediabetes is one possible manifestation of the metabolic syndrome [90]. Insulin resistance and beta-cell failure both contribute to elevated glucose concentrations in prediabetes [91]. Despite the high frequency of obesity in prediabetes and type 2 diabetes, just as “lean” type 2 diabetes has been described [92], so has “lean” prediabetes been described [93]. The pathogenesis of lean type 2 diabetes may be very different than the usual forms of type 2 diabetes.

Many studies of adverse outcomes associated with prediabetes document that not all “definitions” or “stages” of prediabetes (IFG versus IGT versus IFG plus IGT, and HbA1c of 5.7 to 6.4%) equally identify the same magnitude of increased risk for such adverse outcomes. Although not universal, many people that progress from normoglycemia to type 2 diabetes display IGT as their initial glycemic lesion followed by combined IFG and IGT, and finally, their A1c rises [Figure 3] [18,19,94–97].

The atherogenic potential of prediabetes has been recognized for over a quarter century [98]. Even before type 2 diabetes is diagnosed, the prediabetic state is damaging large and small blood vessels [99]. Traditional risk factors for large- and medium-sized vascular disease are active and important in the prediabetic state [100]. While hyperglycemia is the major risk factor for retinopathy, nephropathy and neuropathic disease, traditional atherosclerotic risk factors (e.g., hypertension and hypercholesterolemia) are the predominant influences on the development of macrovascular disease in persons with prediabetes [96,100]. One retrospective cohort study found that persons with prediabetes were at similar risk of developing MI, stroke, and chronic kidney disease as persons with type 2 diabetes [101]. This suggests that prediabetes may be more serious than previously suspected if the risk of such adverse outcomes is as likely in persons with prediabetes as in persons with type 2 diabetes. In persons who suffer an acute cardiovascular complication (e.g., MI or stroke), just as diabetes can reduce the likelihood of full recovery, there are some data suggesting that prediabetes also may reduce the likelihood of recovery from such acute events [102].

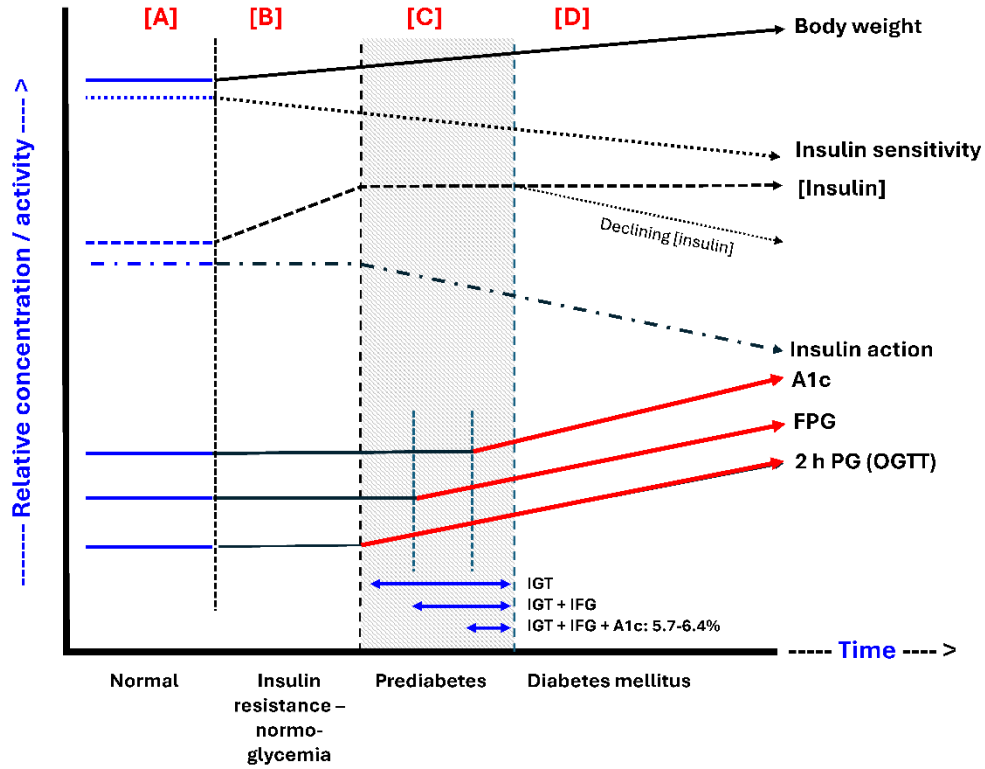

Figure 3. A common natural history of prediabetes and type 2 diabetes can be conceptualized as follows [18,19,94–97]: [A] Normal: Initially, body weight is not excessive, and insulin sensitivity, insulin concentrations, insulin action, 2-h plasma glucose (on OGTT testing; 2 h PG), fasting plasma glucose and A1c are all normal. [B] Insulin resistance—normoglycemia: With weight gain (with excessive adipose tissue), insulin sensitivity declines but insulin action is maintained sufficiently to prevent hyperglycemia because of compensatory beta-cell hyperinsulinism. Reduced insulin sensitivity also marks the beginning of the metabolic syndrome which usually precedes the diagnosis of type 2 diabetes. [C] Prediabetes: Further declines in insulin sensitivity are not adequately compensated because beta-cell insulin production does not continue to increase (or plateaus or declines). At this point, insulin action declines. Reduced insulin action will initially reduce glucose tolerance witnessed in a rise in the 2-h plasma glucose assessed during a standard OGTT. With a PG of 140–199 mg/dL during the OGTT (assuming that diabetes mellitus is not otherwise diagnosed), impaired glucose tolerance (IGT) is present. The next glucose abnormality is a rise in the fasting PG to 100–125 mg/dL that marks the appearance of impaired fasting glucose (IFG) that often occurs together with IGT. Later in prediabetes, A1c rises (once the threshold of 6.5% is met or exceeded, the A1c is in the hyperglycemic range). [D] With continued failure of beta-cell insulin compensation in response to worsening insulin resistance, insulin action has declined sufficiently that diabetes mellitus is diagnosed.

The recognition of prediabetes in an individual can allow intervention that might delay or prevent the development of type 2 diabetes [86]. Without intervention, 5% to 10% of persons with prediabetes will yearly cross glycemic thresholds leading to the diagnosis of type 2 diabetes [86].

Even within the "normoglycemic" range, increasing concentrations of A1c predict increased risks of coronary heart disease, stroke and death from any cause [103]. Of note, increasing A1c levels, even within the reference interval, increased the likelihood of CVD, and were superior to measurements of FPG, random PG or post-challenge PG in this prediction [104]. Collectively, these findings emphasize that the risk of adverse macrovascular, microvascular and neuropathic outcomes increases continuously as patients progress from normoglycemia to prediabetes to type 2 diabetes.

A question that remains is whether prediabetes should be classified as a "disease". Adapted from the National Cancer Institute (NCI) [105], disease is defined as "an abnormal condition that affects the structure or function of part or all of the body and is usually associated with specific signs and symptoms". Because prediabetes is strongly associated with vascular and neuropathic disorders, prediabetes does meet such a definition of "disease." Strengthening this opinion is the fact that prediabetes has a billable ICD-10 code (R73.03) in the United States [106].

Prediabetes is very common (and more common than type 2 diabetes) and its frequency is rising [107]. The CDC reports that ~1/3 of adults have prediabetes and nearly half of individuals aged 65 and above have

prediabetes. Regardless of whether or not taxonomists label prediabetes as a "disease," prediabetes demands the attention of all practitioners [108]. A large number of emerging markers including metabolomics, novel lipid parameters, host-microbe dynamics, and inflammatory markers are being examined [109–113] that may foster a personalized medicine approach to the diagnosis, prognosis, treatment and prevention of prediabetes [114].

Author Contributions

Both authors contributed equally to the manuscript submitted. S.T.O. wrote Sections 2 and 4; W.E.W. wrote Sections 3 and 5 (conclusions). The introduction (Section 1) was authored jointly by S.T.O. and W.E.W. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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