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REVIEW

Diabetes Research and Metabolism

Prediabetes and its link to cardiovascular disease: A narrative review

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Abstract

Prediabetes is a state of "intermediate hyperglycaemia" involving conditions like impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and people with glycated haemoglobin (HbA1c) between 39-47 mmol/mol (5.7-6.4%). Although the diagnostic criteria used to define prediabetes is not uniform worldwide, it still remains a high risk state for developing type 2 diabetes (T2D) with a yearly conversion rate of 5-10%. The pathophysiological defects like obesity, metabolic syndrome, insulin resistance and systemic inflammation that underlie T2D have now been increasingly recognised in patients with prediabetes. Most patients also have co-existing dyslipidaemia, hypertension and a prothrombotic state and these factors aggregate together and impart a high risk for development of atherogenesis and cardiovascular disease (CVD). Over the last decade, several studies have linked prediabetes to macrovascular disease and its subtypes but the evidence also suggest prediabetes to be a flexible and heterogeneous state and multiple mechanisms co-exist with dysglycaemia to cause vascular disease. Intensive life style changes and pharmacotherapy have demonstrated that progression of prediabetes to T2D is preventable and this raises hope for the possibility of concomitant prevention of CVD and its related morbidity and mortality. This narrative review explores the concept of prediabetes and its links to CVD and also investigates the impact of intervention strategies on progression of disease and vascular outcomes.

Keywords: *prediabetes, type 2 diabetes, IFG, IGT, cardiovascular disease*

Introduction

Prediabetes is a contentious concept that describes levels of glycaemia that are above the normal range but below the threshold used to define diabetes. The term principally recognizes individuals at high risk of developing overt diabetes who therefore would benefit from lifestyle interventions to prevent or delay the onset but many people diagnosed with prediabetes may spontaneously revert to normoglycaemia without any intervention [1]. Historically, prediabetes comprised of heterogeneous states of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or elevated glycated haemoglobin (HbA1c) but each of these conditions may have different underlying pathophysiologies [2]. The definition of prediabetes has changed over time and different organization have adopted different diagnostic criteria and "cut-off" points (Table 1) [3-6]. Although World Health Organization (WHO), American Diabetes Association (ADA) and National Institute for Health and Care Excellence (NICE) use the same threshold for defining IGT, ADA uses a lower threshold for defining IFG. Additionally, ADA, International Expert Committee (IEC) and NICE also uses HbA1c cut-off values to identify individuals with prediabetes and overt diabetes. It is not clear which diagnostic criteria would be most appropriate in identifying population with prediabetes but the populations identified by each method may vary widely and therefore it would be difficult to ascertain the true global burden of prediabetes.

Table 1. *Diagnostic criteria for prediabetes according to different organization*

Criterion	WHO	ADA	IEC	NICE
Fasting plasma glucose (FPG)	6.1 - 6.9 mmol/L (110 - 125 mg/dL)	5.6 - 6.9 mmol/L (100 - 125 mg/dL)		6.1 - 6.9 mmol/L (110 - 125 mg/dL)
2 Hour OGTT	≥ 7.8 and < 11.0 mmol/L (140 - 200 mg/dL)	7.8 -11.0 mmol/L (140 - 200 mg/dL)		7.8 - 11.0 mmol/L (140 - 200 mg/dL)
HbA1c	-	39 - 47 mmol/mol (5.7 - 6.4%)	42 - 47 mmol/mol (6.0 - 6.4%)	42 - 47 mmol/mol (6.0 - 6.4%)

The International Diabetes Federation (IDF) have stated that the estimated global prevalence of IGT in individuals between 20-79 years of age was 7.3% (352.1 million persons) in 2017 which would increase up to 8.3% (587 million) by 2045 [7]. The unadjusted prevalence rates were highest in North America and Caribbean (15.4%) and also in Central and South America (10%) whereas the lowest rates were in Europe (5.5%) and South East Asia [7]. In the UK, prediabetes is usually diagnosed on the basis of an HbA1c level (42-47 mmol/mol) and it is estimated that around 7 million people have this condition [8]. The prevalence rate in England increased from 11.6% to 35.3% from 2003 to 2011 or 1 in 3 people were living with prediabetes during that period [9].

It is estimated that 5-10% of people with prediabetes will develop type 2 diabetes (T2D) each year with a similar percentage reverting back to normoglycaemia [2]. The conversion rate varies by the

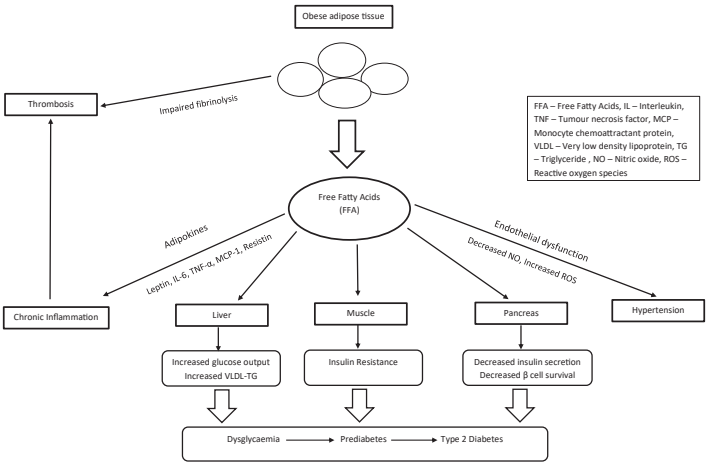

Figure 1. *Metabolic pathways linking Obesity, Metabolic Syndrome, Prediabetes and risk of Atherosclerotic Cardiovascular Disease (ASCVD).*

population characteristics and the definition of prediabetes. Some studies have suggested that the risk of diabetes development on the basis of FPG and 2-hour post load glucose is broadly similar to that posed by HbA1c [10,11]. An ADA expert panel have estimated that up to 70% of individuals with prediabetes will eventually develop diabetes [2]. A complex array of factors determines the progression of prediabetes into overt T2D. Ethnicity play a key role but other factors like life expectancy, socioeconomic status, wealth, access to health care services, obesity, education, public health awareness and initiatives will also influence the prevalence and rate of progression [12,13]. Phenotypic variations amongst people with fasting or post challenge hyperglycaemia may also influence the natural history of progression as individuals with combined IFG + IGT may have a higher rate of progression to T2D in comparison to patients with IFG alone [14].

Prediabetes and risk of cardiovascular disease

IFG, IGT and T2D form a continuum of dysglycaemia. The pathophysiological defects which underlie T2D are also being increasingly recognized in a pre-diabetic state [15]. With progression of dysglycaemia, patients tend to develop marked visceral obesity, insulin resistance (IR) and exhibit progressive beta cell failure leading to impaired insulin secretion. Furthermore, pre-diabetic state also includes increased lipolysis, decreased endogenous levels of glucagon like peptide 1 (GLP-1) and impaired suppression of postprandial glucagon levels [16,17]. These factors accelerate the development of metabolic syndrome and promotes the release of a variety of adipokines, pro-inflammatory cytokines and intracellular adhesion molecules from adipose tissues that seemingly elicit metabolic risk factors that predispose to both prediabetes and cardiovascular disease (CVD) (Figure 1) [18-20]. Endothelial dysfunction occurs early in the pathogenesis of atherosclerosis and predicts future cardiovascular (CV) events. As endothelial cells take up glucose through the insulin dependent carrier glucose transporter 1 (GLUT-1), hyperglycaemia induced endothelial dysfunction precedes development of T2D and is seen in both IFG and IGT [21,22]. Additionally, increased deposition of advanced glycation end products (AGE's), availability of excess free fatty acids and impaired endothelial nitric oxide (NO) generation also contributes to endothelial dysfunction, increased endothelial permeability and poor vasodilation [23-25]. Other factors like activation of renin-angiotensin-aldosterone system (RAAS) induced accentuated vascular IR [26], impaired vascular fibrinolytic balance [27] and reduced microvasculature flow [28] also play a key role in pathogenesis of atherosclerotic cardiovascular disease (ASCVD) in prediabetes.

Historical evidence linking IFG and IGT with cardiovascular disease

Hyperglycaemia is a well-established risk factor for CVD [29,30]. T2D have been also recognised as an independent risk factor for CVD [31], but since the process of IR sets in several years before T2D is diagnosed, patients with prediabetes may also have a similar risk of developing CVD. The long unresolved debate that persist is whether elevated glucose is a direct cause of atherosclerosis or clinical CVD? IGT have been associated with increased risk of CVD and the shape of the relationship is linear [32,33]. In contrast, the association of IFG and CVD risk is far more unclear and the relationship is usually non-linear [33,34]. Interestingly, most prospective studies employ a single determination of glycaemic status at baseline, therefore the most pertinent question arises as to whether the risk of developing CVD is confined to people with prediabetes who develop diabetes or whether the risk is still increased amongst people even if they never develop diabetes? Additionally, the cut-offs used by the ADA and WHO for defining IFG and IGT at different time periods may not only led to increase in the prevalence of prediabetes but it also necessarily augmented the risk estimates of CVD associated with such conditions [34-36]. Even if we accept that prediabetes imparts a modest increase risk for CVD, this doesn't prove that glucose alone directly causes atherosclerosis and its complications. We should be able to dissect away the key confounding variables like obesity, hypertension, dyslipidaemia, pro-inflammatory and pro-thrombotic state as most of these are components of metabolic syndrome is usually present in patients with prediabetes [37].

Over the last 15-20 years several studies have established the link between IFG and IGT with CVD or CHD risk. Levitzky et al. [38] showed an association of IFG (defined by 1997 and 2003 ADA definition) with increased CHD risk and CVD events (IFG defined by 1997 definition) whereas Lee et al. [39] showed that increasing fasting glucose (FG) in non-diabetic population is associated with higher, rapid and more severe risk of MI, stroke and all-cause mortality. Shin JY et al. [40] demonstrated association of aggravation of arterial stiffness (measured by Ba-PWV – brachial ankle pulse wave velocity) with high normal fasting plasma glucose (FPG) in non-diabetic subjects but others didn't find IFG to be a major determinant for CVD and CHD related mortality [33,41]. IGT predicted by 2-hour post load glucose was found to be the strongest predictor for CVD, CHD and all-cause mortality by several authors [33,41,42]. Karbek et al. [43] established both IFG and IGT to be associated with increased CV risk assessed by serum highly sensitive C-reactive protein (hsCRP) and carotid intima media thickness in comparison to controls and similarly Hadaegh et al. [44] demonstrated a higher independent risk of silent CAD in female patients with IFG and IGT in comparison to male patients. In contrast, Kiviniemi et al. [45] in their prospective observation study have shown that risk of CAD in patients with prediabetes (IFG and IGT) was comparable to those with CAD and normoglycaemia but definitely lower than patients with T2D when treated with revascularization, optimal medical therapy or both.

Multiple meta-analyses have used different definitions of IFG with or without IGT to evaluate the risk of or find associations between prediabetes and CHD/CVD. Ford et al. [46] found a modest increase in risk of CVD with IFG [estimated relative risk (RR) – 1.12 to 1.37) and IGT (estimated RR – 0.97 to 1.30) but the

Table 1. *Studies evaluating association between prediabetes (defined by HbA1c criteria) and cardio-metabolic risk profile.*

Author, Year, Type	Study population	Objective	Key findings / Results	Conclusion
Di Pino et al, 2014, Observational cross-sectional design 56	"274 subjects attended hospital for diabetes and CV risk evaluation. All had OGTT and HbA1c estimated. Patients were classified as per HbA1c levels: HbA1c < 39 mmol/mol – controls (n=97) HbA1c 39-46 mmol/mol – prediabetes (n=117) HbA1c ≥ 48 mmol/mol – Type 2 diabetes (n=60)"	To investigate CV risk profile in subjects with prediabetes and also to assess whether HbA1c is a better indicator of CV risk compared to glucose homeostasis parameters such as fasting and 1 or 2 h post OGTTs.	" Subjects with prediabetes were older and had higher SBP, DBP, FPG, TG's, HOMA-IR, hs-CRP and lower HDL than the controls. - Most patients with 1 h glucose > 8.6 mmol/l had HbA1c between 39-46 mmol/mol. "	"HbA1c is a better marker to identify prediabetic subjects at high CV risk compared to fasting glycaemia or OGTT alone. -1 h post load glucose may be a better glycaemic marker of vascular damage. "
Piveta VM et al, 2014 Observational cross sectional design 57	514 subjects who underwent coronary angiography for variable reasons (stable angina, positive stress test, preoperative evaluation etc.) All had glycaemic status assessed by FPG and HbA1c 10 year risk of CAD was calculated using the Framingham risk score (FRS)	To study cardio metabolic risk profile of patients with prediabetes identified either by FPG or HbA1c	Subjects with prediabetes as per FPG criteria had higher insulin resistance and lower β cell function (by HOMA indexes) and similar FRS (>20%) in comparison to normal subjects. As per HbA1c criteria, subjects with prediabetes had higher FPG but HOMA indexes didn't differ. They also had higher proportion of FRS (>20%), hypertension and dyslipidaemia in comparison to normoglycaemic counterparts.	-Individuals with prediabetes identified by HbA1c have a worse cardio metabolic risk profile assessed by FRS when compared to normoglycaemic subjects.
"Giraldez-Garcia C et al, 2015 The PREDAPS study Cross sectional analysis 68015"	"2022 patients with prediabetes recruited from the PREDAPS study cohort. Patients were grouped as: Normoglycaemia – FPG < 5.6 mmol/l; HbA1c < 39 mmol/mol (n=838) Isolated HbA1c = FPG < 5.6 mmol/L; HbA1c – 39-46 mmol/mol (n=316) Isolated FPG = FPG – 5.6-6.9 mmol/L; HbA1c < 39 mmol/mol (n=254) AND Both criteria group = FPG – 5.6-6.9 mmol/l; HbA1c – 39-46 mmol/mol (n=614	To examine the cardio metabolic risk profile in patients with prediabetes defined by FPG and/or HbA1c	A linear trend was observed in BMI, WC, SBP, DBP, HDL, TG's and uric acid when groups were compared with highest absolute values were in the group with both criteria for prediabetes. Similarly, the frequency of metabolic syndrome also showed a linear trend with highest absolute frequency was in the group with both criteria (76.2%) in comparison to subjects with normoglycaemia (15%).	-Individuals with prediabetes defined by FPG and HbA1c had worst cardio metabolic profile while individuals defined by either FPG or HbA1c have an intermediate cardio metabolic profile in comparison to subjects without prediabetes.
Woo YC et al, 2015 Follow up observational design 59	"1300 patients returning for the fourth visit of the Hong King Cardiovascular Risk Factor Prevalence Study (CRISPS4) Subjects were subdivided as per their glycaemic status according to ADA 2010 criteria "	To investigate the usefulness of the additional measurement of HbA1c compared with performing only OGTT in identifying participants at increased cardio metabolic risk	Application of HbA1c criteria increased the proportion of patients diagnosed with diabetes (7.8%) and prediabetes (65.3%) in comparison to doing OGTT alone -Subjects with raised HbA1c and normal glycaemia had WC, SBP, FPG, HOMA-IR, Gutt Index and FRS intermediate between those with normal HbA1c and glycaemia and those with IFG and/or IGT (all p <0.01)	HbA1c criteria in addition to OGTT results will detect large number of patients with prediabetes with non-favourable cardio metabolic profile. These at risk participants and would benefit from early preventative interventions

CV – Cardiovascular; OGTT – Oral Glucose tolerance test; HbA1c – Glycated haemoglobin; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; FPG – Fasting plasma glucose; TG's – Triglycerides; HOMA-IR- Homeostatic Model Assessment of Insulin Resistance; hs-CRP- highly sensitive C reactive protein; HDL- high density lipoproteins; CAD – Coronary artery disease; FRS- Framingham Risk Score; BMI- Body Mass Index; WC-Waist Circumference; ADA-American Diabetes Association; IFG-Impaired fasting hyperglycaemia; IGT- Impaired glucose tolerance.

risk with IFG (110 mg/dl, RR – 0.65 to 2.5) was higher than IFG (100 mg/dl, RR – 0.87-1.40). Bancks et al. [47] observed a higher risk of CVD in men (55 years through to 85 years) with FG of 6.3 - 6.9 mmol/L in comparison to men with FG < 5 mmol/L and groups who transformed from normal FG to diabetes over 4 years had higher CVD risk (1.3 - 3.6 fold) than those who didn't. Likewise, Huang Y and colleagues [48] have reported a higher risk of CVD in patients with different definitions of prediabetes (IFG-ADA; RR 1.13, IFG-WHO; RR 1.26 and IGT; RR 1.30) in comparison to normoglycaemic patients. Huang Y et al. [49] have also established a higher risk of all cause and cardiovascular mortality with IFG (110 mg/dl, RR 1.12 and 1.19), IGT (RR 1.33 and 1.23) and IFG (110 mg/dl) combined with and/or IGT (RR 1.21 for both mortalities) but the risk was less with IFG (100 mg/dl). Xu T et al. [50] reported an increased risk of CHD with different IFG criteria [100 mg/dl; RR 1.11 (1.02-1.21) and 110 mg/dl; RR 1.18 1.1-1.28) but suggested that 2-hour plasma glucose (PG) and other CV risk factors are needed for complete risk stratification. Similarly, Zhao Y et al. [51] have demonstrated that prediabetes is associated with higher risk of major adverse cardiovascular event (MACE) in CAD patients after percutaneous coronary intervention (PCI) [adjusted RR 1.53 (1.25-1.87); p<0.001] in comparison to patients with normoglycaemia. Two meta-analyses studied the association between prediabetes and stroke. Lee M et al. [52] established a future higher risk of stroke with IFG [110-125 mg/dl; summary estimate (SE) 1.21 (1.02-1.44); p=0.03] and with IGT alone or in combination with IFG [SE 1.26 (1.1-1.43); p< 0.001] whereas Pan Y et al. [53] showed and increased risk of stroke with prediabetes [Hazard ratio (HR) 1.42 (1.13-1.8); p=0.003] and poor outcome [HR 1.33 (1.11-1.59); p=0.002] but not all cause mortality [HR 1.69 (0.84-3.4); p=0.14] in comparison to normoglycaemic counterparts.

Prediabetes (defined by HbA1c criteria) and cardiovascular disease

The glycaemic measures that are used to identify prediabetes represents a different domain of glucose metabolism. While FPG reflects basal dysglycaemia, HbA1c reflects chronic exposure to basal and postprandial hyperglycaemia [54]. HbA1c has several advantages over FPG and oral glucose tolerance test (OGTT) results, including feasibility and pre-analytical stability, less day to day biologic variations and is more clinically convenient [5]. It has been pointed out that some characteristics such as sex, race and age of individuals with prediabetes vary by the glycaemic measure [55]. Therefore, there may be differences in the cardio metabolic risk profiles of individuals according to glycaemic measure used to evaluate the presence of prediabetes. Two observational cross sectional studies [56,57] (Table 2) explored the relationship between cardio-metabolic risk and prediabetes defined by HbA1c. Di Pino et al. [56] established HbA1c as a better marker to identify prediabetic subjects at high risk of CVD in comparison to patients identified by fasting or 2Hr PG on OGTT. Similarly, Piveta et al. [57] demonstrated worsening cardio-metabolic risk profile [assessed by Framingham risk score (FRS)] in prediabetic subjects defined by HbA1c criteria who underwent coronary angiography in comparison to patients with normoglycaemia. In the PREDAPS study, Giraldez-Garcia C et al. [58] reported a worse cardio-metabolic profile in prediabetic patients when both FPG and HbA1c criteria was used to define them in comparison to prediabetic patients defined by FPG or HbA1c criteria or patients without prediabetes. Finally, Woo YC et al. [59] observed 1300 patients during their 4th visit for the CRISPS4 follow up study and established that application of HbA1c criteria in addition to OGTT criteria identified a greater proportion of patients with prediabetes and these patients also had a less favourable cardio-metabolic profile and were candidates for early intervention (Table 2).

HbA1c has been associated with microvascular disease [60], but the correlation with macrovascular disease is less clear and poorly understood [36,61,62]. High HbA1c levels have been also strongly linked with CVD in people with [63] or without diabetes [61,64] however the association between low HbA1c levels in people without known diabetes and CVD risk still remain a matter of intense debate. In the last 5-6 years, several studies (Table 3) [65-71] have reported an increased association of prediabetes defined by HbA1c with atherosclerosis, risk and actual event of CVD and all-cause mortality, but the biological mechanisms underlying this association is mostly unknown whereas others didn't show an additional role for HbA1c in predicting CVD risk in individuals with prediabetes [62,71]. In the Dallas Heart Study 2 (DHS-2), Xing FYF et al. [65] established a higher prevalence of subclinical coronary and carotid atherosclerosis in patients with prediabetes defined by HbA1c and/or FPG criteria. Likewise, subjects with prediabetes (defined by ADA HbA1c criteria) from the ILERVAS project were found to have higher prevalence of subclinical atheromatous disease evidenced by higher plaque burden and greater number of affected territories [70]. Kim HK et al. [67] identified a greater number of individuals at high risk of developing CVD by using either HbA1c criteria alone or in combination with FPG to define prediabetes. Similarly, Warren B et al. [68], established that participants defined by HbA1c based definitions had a higher hazard ratio for developing chronic kidney disease (CKD), CVD, peripheral arterial disease (PAD) and all-cause mortality in comparison to patients with other definitions for prediabetes. Finally, Vistisen D et al. [69], demonstrated that the worst prognosis for a major event (fatal/non-fatal CVD or all-cause mortality) were in subjects with prediabetes defined by HbA1c in comparison to subjects with normoglycaemia or when prediabetes was defined by FPG or 2h PG criteria.

Prevention of progression of prediabetes to diabetes and reducing CVD risk

The rationale for identifying those with prediabetes is to intervene and prevent development of two major detrimental outcomes, progression to T2D and reduce risk of macrovascular disease. Prediabetes alone may not be the sole reason for premature atherosclerosis and its complications therefore diabetes prevention may not be sufficient to prevent CVD and related mortality. Nonetheless, most people with prediabetes have metabolic syndrome which unequivocally is a major risk factor for macrovascular disease. Therefore, it is perfectly reasonable to intervene to address all CVD related risk factors in patients with prediabetes.

The opportunity to offer evidence based life style intervention programme to such high risk individuals sounds quite appealing

Author, Year, type	Study population	Objective	Key findings/Results	Conclusion
Xing FYF et al, 2014, longitudinal follow up study 65	Dallas Heart Study 2 (DHS-2), subset of DHS 1 study 2340 participants without prevalent diabetes defined by self-report, medication history or HbA1c and FPG values	To evaluate the joint associations of HbA1c and FPG with prevalent subclinical coronary and carotid atherosclerosis	Patients with prediabetes (HbA1c and/or FPG criteria) had higher crude prevalence of CAC (33% vs. 22%; p<0.001) and higher mean carotid wall thickness (1.32 vs. 1.29 mm; p<0.001)	Prediabetes is crudely associated with markers of diabetic macrovascular disease in presence of other CV risk modifiers
Goto A et al, 2015,Prospective follow up design 66	The Japan public health centre based prospective study (JPHC) 29,059 participants without diabetes, data collected during health check-ups	To clarify the association between HbA1c levels and CVD risk among people without known diabetes	During median follow up of 9.4 years, 935 CVD events occurred (770 strokes, 165 CHD's) HR for CVD's as per categories of HbA1c were: - < 5% – 1.5 [1.15-1.95] -6.054 - 5.5-5.9 % - 1.01 [0.85-1.2] - 6.0-6.4 % - 1.04 [0.82-1.32] ≥ 6.5% - 1.77 [1.32-2.38], p value for nonlinear trend: <0.001	Both low and high levels of HbA1c were associated with higher risk of CVD in a general population without diabetes
Kim HK, et al, 2016, Prospective follow up design 67	76434 South Koreans who underwent a general health examination in the Health Screening & Promotion Centre	To compare the association between CVD and prediabetes defined by FPG, HbA1c or their combination	Age and sex adjusted HR for CVD events for prediabetes defined by -FPG only – 1.19 [1.08-1.31] -HbA1c only – 1.28 [1.16-1.42] -combined criteria – 1.20 [1.09-1.32] -After adjustment for multiple risk factors, HR's for overall CVD events were significantly high with prediabetes defined by HbA1c or combined criteria	Adding HbA1c in defining prediabetes has a certain role in detecting individuals with high risk of CVD
Warren B et al, 2017, Prospective cohort study 68	10,844 ARIC study participants without diagnosed diabetes who attended visit 2 and 7194 participants who attended visit 4	To compare the risk of future outcomes (incident diabetes, CKD, atherosclerotic CVD, PAD and all-cause mortality) across different definitions of prediabetes	-ADA FPG criteria was most sensitive for major clinical outcomes -After demographic adjustments, HbA1c based definitions had higher HR's and better risk discrimination for CKD, CVD, PAD and all-cause mortality -HbA1c was better than glucose based definitions for demonstrating significant overall improvement for CV outcomes	HbA1c defined prediabetes were more specific and provided modest improvements in risk discrimination for clinical complications
Vistisen D, et al, 2018, Prospective cohort study design 69	5427 participants from the Whitehall II study, an occupational cohort of British Civil servants without diabetes	To compare risk of CVD and all-cause mortality in prediabetes defined by FPG, 2hPG and HbA1c Major event defined as non-fatal/fatal CVD or all-cause mortality	- Compared to normoglycaemia, prediabetes, incident rate for major event was 54% and 37% higher by WHO/IEC and ADA criteria respectively -Incident levels as per HbA1c levels were 5.7-6.4% (ADA) – 26% 6.0-6.4% (IEC) – 29.5% Which are approx. twice the rate in normoglycaemic group -10 year absolute risk for an event was higher for all levels of HbA1c and comparable for FPG and 2hPG	Prediabetes defined by HbA1c was associated with worse prognosis for a major event This is mainly due to clustering of other cardio metabolic risk factors with hyperglycaemia

Author, Year, type	Study population	Objective	Key findings/Results	Conclusion
Sanchez E et al, 2019, cross sectional design 70	6688 nondiabetic subjects without CVD recruited from the ILERVAS project, a trial dealing with subclinical atheromatous disease	To characterize atheromatous plaque burden by number of affected territories and total plaque area in prediabetes stage (defined by ADA HbA1c criteria)	-Prevalence of subclinical atheromatous disease with higher in prediabetes compared to patients with HbA1c < 5.7% (70.4 vs 67.5%; p=0.017) -Prediabetes was associated with higher number of affected territories (2[1;3] vs. 1[0;3],p=0.002) -Atheromatosis is magnified (p=0.016) in subjects with 3 or more CV risk factors	Prediabetes is accompanied by an increased risk of atheromatous disease It also modulates the atherogenic effect of CV risk factors in terms of distribution and total plaque area in a sex dependent manner

DHS 1 and 2 – Dallas Heart Study 1 and 2, HbA1c – Glycated haemoglobin, FPG- Fasting plasma glucose, CAC- Coronary artery calcium, CV-Cardiovascular, CVD-Cardiovascular disease, CHD-Coronary heart disease, HR- Hazard ratio, ARIC- Atherosclerosis Risk in communities, CKD-Chronic kidney disease, PAD- Peripheral artery disease, ADA- American Diabetes Association, 2hPG- 2 hour plasma glucose, WHO-World Health Organisation, IEC- International Expert Committee, ILERVAS- Assessing the prevalence of subclinical vascular disease and hidden kidney disease.

on paper but the real world experience is often met with multiple barriers and roadblocks. As these programmes will be principally delivered in primary care, robust and adequately resourced public health, referral pathways, dietary policies, exercise schemes and willingness and acceptance from the public is necessary to make such intervention programmes effective and successful. Several lifestyle intervention studies have demonstrated decreased progression of prediabetes to T2D. The Finnish Diabetes Prevention study group showed reduced cumulative incidence of diabetes in patients with IGT after 4 years with life style changes in the intervention group (11%, 95% CI 6-15%) in comparison to the control group (23%, 95% CI 17-29%). The risk of diabetes was also found to be reduced by 58% (p<0.001) in the intervention group [72]. The National Diabetes Prevention Program (DPP) was a 3-year intervention plus 3 years of follow up activities. After 3.2 years, the DPP showed a 71% decrease in the incidence of diabetes in lifestyle intervention participants aged 60 years or older compared with control group [73]. The Da Qing IGT and Diabetes study, a 6-year intervention study in subjects with IGT showed lowered cumulative incidence of diabetes in the diet group (43.8%, 95% CI 35.5 - 52.3%), exercise group (41.1%, 95% CI 33.4-49.4%) and diet plus exercise group (46.0%, 95% CI 37.3-54.7%) in comparison to control group (67.7%, 95% CI 59.8-75.2%) [74]. Other authors have made cautious suggestions that such interventions may have some benefit in delaying or preventing the onset of diabetes [75,76]. On the contrary, a large scale randomised controlled study in a UK community setting failed to show a statistically significant reduction in progression to T2D at 3 years with diabetes prevention lifestyle intervention (Let's Prevent) in comparison to normal care. A subgroup of patients who engaged and attended most intervention sessions did show a significant reduction in progression to diabetes [77].

Several pharmacotherapies have also shown potential benefits in risk reductions for development of overt T2D from prediabetes. The key studies that have shown substantial benefits are: STOP-NIDDM trial (Acarbose, 25% risk reduction (RR) after 3.3 years in IGT) [78], DREAM (Rosiglitazone, 62% RR after 3 years in IGT and/or IFG) [79], ACT-NOW (Pioglitazone, 72% RR over 2.4 years in IGT), [80] CANOE (Rosiglitazone and Metformin, 26% RR after 3.9 years in IGT) [81], IDDP 1 (Metformin, 26.4% RR after 30 months in IGT) [82] and IDDP 2 (Pioglitazone, 28% RR in IGT) [83]. A meta-analysis by Phung OJ et al. [84] of 13 studies with 11,600 participants showed that use of oral hypoglycaemic agents in patients with prediabetes double the odds of achieving normoglycaemia in comparison to controls [Odds ratio (OR) 2.03, 95% CI 1.54-2.67)]. Individually, only thiazolidinedione's (OR 2.33, 95% CI 1.93-2.81) and α glucosidase inhibitors (OR 2.02, 95% CI 1.26-3.24) was associated with significantly increased odds and not biguanides (OR 2.04, p=0.06) or sulfonylureas (OR 1.84, p=0.39) [84].

Although the evidence surrounding delay in progression of prediabetes to T2D with interventions are quite robust, very few studies have actually been conducted to demonstrate whether lifestyle or pharmacological interventions have any role in reducing cardiovascular risk in people with prediabetes. The Diabetes Prevention Program Outcomes Study (DPPOS) [85] evaluated the impact on intensive lifestyle interventions in patients with prediabetes who were at high risk of CVD (53% had metabolic syndrome). The investigators demonstrated that over a course of 10 years, the CVD risk (measured by Framingham 10 year CVD risk scores) decreased for people with prediabetes (scores reduced by 18.6% in year 1 vs. 15.9% in year 10, p<0.01). The effect was more pronounced when people had regression from prediabetes to normal glucose regulation (NGR) over the course of time [85].

The evidence surrounding pharmacological intervention leading to cardiovascular benefits in individuals with IGT was first established in the STOP-NIDDM trial [78]. Acarbose therapy was associated with a 34% relative risk reduction for hypertension (HR 0.66, 95% CI 0.49-0.89; p=0.006) and 5.3% absolute risk reduction (ARR). It also led to 49% relative risk reduction in development of cardiovascular events (HR 0.51, 95% CI 0.28-0.95; p=0.03) and 2.5% ARR. Among CV events, the major reduction was in the risk of myocardial infarction (HR 0.09, 95% CI 0.01-0.72; p=0.02) [78]. The ORIGIN trial showed a neutral effect of early initiation of basal insulin glargine on CV outcomes in patients with patient with IGF/IGT [86]. The NAVIGATOR study group used nateglinide, an insulin secretagogue in 9306 participants with IGT. In comparison to a placebo, nateglinide didn't significantly reduce the cumulative incidence of core composite CV outcomes (HR 0.94, 95% CI 0.82-1.09; p=0.43) or the extended composite CV outcome (HR 0.93, 95% CI 0.83-1.03; p=0.16) [87]. In a meta-analysis, Hopper et al, didn't find any difference in risk of all-cause mortality in the intervention vs. control group (HR 0.96, 95% CI 0.84-1.10) or on CV death, fatal or non-fatal myocardial infarction or stroke [76]. Finally, Liao et al. [88] in their systematic review and meta-analysis of 9 trials with 12026 patients showed that addition of pioglitazone to standard therapy was associated with lower risks of major adverse cardiovascular events (MACE) (RR 0.77, 95% CI 0.64-0.93) and myocardial infarction (RR 0.68, 95% CI 0.49-0.96) in patients with prediabetes or insulin resistance. Pioglitazone was

also associated with a trend towards reducing recurrent stroke risk (RR 0.81, 95% CI 0.65-1.01) in the same population. However, use of pioglitazone was associated with increased risks of heart failure, bone fracture, oedema and weight gain [88].

In conclusion, CVD is the leading cause of morbidity and mortality in patients with dysglycaemia. The progression of normoglycaemia to prediabetes and then to overt diabetes is a disease continuum as the underlying pathophysiological mechanisms that impart IR and impair insulin secretion and sensitivity is very similar and tends to deteriorate over time. Moreover, in association with other vascular risk factors, it augments the risk of CVD and related mortality. Early identification and interventions are needed in patients with prediabetes to prevent progression to overt diabetes and also to mitigate chances of development of macrovascular disease and its related complications.

KEY POINTS

- Prediabetes is a prelude to diabetes as the underlying pathophysiological defects like insulin resistance and loss of pancreatic β cell function are similar to T2D
- The classification of prediabetes may widely vary based on criteria chosen to define it, but the HbA1c criteria is now being increasingly recognized to be the standard
- Patients with prediabetes have metabolic syndrome and in association with other risk factors leads to incremental risk of CVD and all-cause mortality
- Early recognition of these high risk patients and intervention with lifestyle modifications and pharmacotherapy can restore normoglycaemia and also lower risk of CVD and associated complications. This requires robust health policies, pathways, care co-ordination, investment, organization and awareness and education of the at risk population

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