Significance of prediabetes as a nosological entity

Ladislav Stepanek^{a,b}, Dagmar Horakova^a, Marie Nakladalova^b, Lubica Cibickova^c, David Karasek^c, Josef Zadrazil^c

Prediabetes is a glucose metabolism disorder considered as a distinct nosological entity which strongly predicts the development of type 2 diabetes mellitus. This nosological entity itself is a serious condition indicating an increased risk of atherosclerotic and oncological complications. In patients with prediabetes, other components of metabolic syndrome are usually present, such as arterial hypertension, obesity or dyslipidaemia, further increasing an individual's risk of morbidity and mortality. Prediabetes is a long-developing disorder which offers enough time for early diagnosis and intervention; it may even be reversible. This review summarizes current knowledge on the definition, detection, epidemiology, cardiovascular and other consequences of prediabetes. It also gives suggestions for future research, along with recommendations for clinical practice.

Key words: prediabetes, impaired fasting glucose, impaired glucose tolerance, prevalence, cardiovascular complications, cancer

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^aDepartment of Public Health, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

^bDepartment of Occupational Medicine, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

^c3rd Department of Internal Medicine – Nephrology, Rheumatology and Endocrinology, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

Corresponding author: Ladislav Stepanek, e-mail: stepanek.ladislav@gmail.com

INTRODUCTION AND DEFINITIONS

Prediabetes is currently a distinct nosological entity characterized by impaired glucose metabolism, with levels that are above normal but fall below the criteria for diabetes mellitus (DM). The term *prediabetes* itself implies a condition preceding the development of type 2 DM (T2DM) which in most cases is true, as seen below. At a quantitative level, however, there is no globally consistent definition as professional societies use different criteria. This complicates the comparison and interpretation of data from various parts of the world, making them less clear. There is even no uniform consensus about the term *prediabetes* which is used mainly by the American Diabetes Association (ADA) (ref.¹). The World Health Organization (WHO), preferring the term *intermediate hyperglycemia*, defined prediabetes as the presence of at least one of the following conditions: (1) impaired fasting glucose (IFG), that is, a condition characterized by fasting plasma glucose (FPG) ranging from 6.1 to 6.9 mmol/L and, at the same time (if measured), 120-minute plasma glucose below 7.8 mmol/L after a 75 g oral glucose toler-

ance test (OGTT); (2) impaired glucose tolerance (IGT), that is, a condition characterized by FPG below 7 mmol/L and, at the same time, 120-minute plasma glucose between 7.8 and 11.0 mmol/L after a standard OGTT (ref.²). The ADA definition of prediabetes has a different lower cut-off for IFG, ranging from 5.6 to 6.9 mmol/L and (since 2010) an additional criterion of glycated hemoglobin A1c (HbA1c) between 39 and 47 mmol/mol (ref.³). Apart from IFG, there are also variations in HbA1c cut-offs, as evidenced, for example, by the 42–47 mmol/mol range used in Canada⁴. Table 1 summarizes the criteria for prediabetes used by various professional societies.

As demonstrated below, it is apparent that professional societies using the criteria with a wider IFG (and HbA1c) range report higher prevalence and lower complication rates of prediabetes. Reversely, a narrower IFG range (with a lower cut-off as the WHO criteria) means lower prevalence and higher complication rates of prediabetes.

So far, HbA1c has not been globally introduced as a criterion of prediabetes. This relatively novel criterion has been assessed by numerous studies, most of which consid-

Table 1. Prediabetes criteria of various professional societies.

	WHO (ref. ²)	ADA (ref. ³)	CDA (ref. ⁴)
At least 1 of the conditions (lines):			
Fasting plasma glucose (mmol/L)	6.1-6.9	5.6-6.9	6.1-6.9
2-hour oral glucose tolerance test (mmol/L)	7.8-11.0	7.8-11.0	7.8-11.0
Hemoglobin A1c (mmol/mol)		39-47	42-47

er this step beneficial, pointing to increased sensitivity of diagnosing prediabetes if HbA1c is used in combination with the above original methods⁵⁻⁹. By contrast, Chillelli et al. reported that in a cohort of 501 individuals, HbA1c (the ADA interval) was not a sufficiently specific marker for the diagnosis of prediabetes¹⁰. Nevertheless, health organizations worldwide agree on a need for standardization of HbA1c diagnostic assays. Therefore, the International Federation of Clinical Chemistry (IFCC) developed a reference measurement procedure based on a concept of metrological traceability to achieve global standardization. According to the IFCC, patients' HbA1c concentrations should be reported using the International System of Units (i.e. in mmol/mol). However, the US National Glycohemoglobin Standardization Program (NGSP) supports reporting HbA1c concentrations differently (in %) based on the Diabetes Control and Complications Trial. These two units can be converted using the following formula¹¹:

$$\text{NGSP (\%)} = 0.0915 \times \text{IFCC (mmol/mol)} + 2.15$$

The three diagnostic methods are not 100 percent concordant with one another. Some studies have shown that FPG alone may be inadequate for detecting prediabetes while higher detection rates were reported when OGTT and HbA1c were used¹². But even these two criteria may be discordant, as suggested by Camacho et al. in their study (n=218) demonstrating a significant difference between these two tests for the diagnosis of prediabetes among Hispanic and non-Hispanic white populations¹³.

The advantages of HbA1c analysis over FPG analysis are independence from the feeding/fasting cycle, lower biological variability of the obtained results and an easier preanalytical phase due to the higher stability of HbA1c. On the other hand, the disadvantages are dependence on the mean erythrocyte life span and also HbA1c interference with pathological forms of hemoglobin during the

analysis process¹⁴. The preanalytical phase is a key part of the FPG determination as various anticoagulants, stabilizing additives and other conditions influence the obtained results. In this way, consistent adherence to standardized measurement procedures is crucial for applying established cut-offs for IFG.

PREVALENCE OF PREDIABETES

While there are estimates of the worldwide prevalence of DM (age-standardized prevalence of 8.5% in 2014) (ref.¹⁵), no such relevant estimates are available for prediabetes. Part of this is surely due to missing data from many regions of the world, together with the globally varied criteria for diagnosing this nosological entity. Glucose metabolism abnormalities have rapidly risen in prevalence in both developed and developing countries of the world¹⁶. Prediabetes is estimated to affect more than 470 million people throughout the world in 2030 (ref.¹⁷). Still at the global level, as many as 7.3% of adults aged 20-79 years suffer from IGT. More than 70% of them live in middle- and low-income countries; one half of them are younger than 50 years of age. By 2045, the number of people aged 20-79 years with IGT is projected to increase to 8.3% (ref.¹⁸). About 7% of the adult population worldwide live with either IGT or IFG. The two abnormalities are estimated to overlap in 25% of Caucasians¹⁷. The global prevalence of IFG is estimated at 5%; however, this is rather tentative given the two criteria for diagnosing IFG (ref.¹²). Globally, the mean FPG levels have been observed to rise. In 2008, global age-standardized mean FPG was 5.50 mmol/L (95% confidence interval [CI] 5.37–5.63) for men and 5.42 mmol/L (5.29–5.54) for women, having risen by 0.07 mmol/L and 0.09 mmol/L per decade, respectively¹⁶. The globally uniform criteria for diagnosing IGT enables an easy comparison of its prevalence in various parts of the world as indicated in Fig. 1.

Fig. 1. Age-adjusted prevalence (%) of impaired glucose tolerance (20-79 years), 2017 (ref.¹⁸).

Data on the prevalence of prediabetes show considerable regional differences. Very accurate data with time trends are obtained from the long-term US population-wide National Health and Nutrition Examination Survey (NHANES). This shows that based on IFG and HbA1c measurements (both the ADA criteria), 33.9% of US adults over 18 years of age had prediabetes in 2015 (48.3% of individuals over 65 years). This corresponds to 84.1 million of prediabetics in the USA in 2015 (ref.¹⁹). Such high prevalence may also be affected by the fact that the ADA criteria has the widest IFG and HbA1c range. The increase in prevalence between the 1999-2002 and 2007-2010 NHANES cycles was higher for females than for males. However, prediabetes is still more prevalent in US males. Remarkably, the prevalence of IFG (the ADA criteria) remained relatively stable, rising from 23.9% to 26.6% between the same cycles, in contrast with HbA1c (the ADA criteria) increasing from 9.5% to 17.8% (ref.²⁰).

Many European countries lack adequate population-representative data for estimating the prevalence of prediabetes. There are certainly great regional variations across Europe in the prevalence of hyperglycemic disorders²¹. Overall, however, as many as 5.5% (36 million) of European adults aged 20-79 years are estimated to live with IGT. By 2045, the prevalence of IGT in Europe is expected to increase to 6.1%. Although this is one of the lowest prevalence rate worldwide, it is disturbing given the significant phenomenon of population aging¹⁸.

PROGRESSION FROM PREDIABETES TO T2DM

Prediabetes is a risk factor for the development of T2DM. Estimates indicate that most individuals (up to 70%) with prediabetes eventually develop T2DM (ref.²²). Data on the annual incidence of progression from prediabetes to T2DM are rather varied, depending on both the prediabetes diagnostic criteria used and conditions or interventions in the studied individuals. When considering data on prediabetics with no targeted intervention, a large meta-analysis of prospective studies (n=29,475) from 1979 to 2004 reported annual incidence rates for the progression of 6.1-9.2% in individuals with isolated IFG (the WHO criteria), 4.4-6.4% in those with isolated IGT and 10-15% for patients with both disorders combined. When these data are summed, the annual incidence of progression from prediabetes to T2DM is 5-10% (ref.²³). The risk of transition from prediabetes to established T2DM is not evenly distributed in the prediabetes diagnosis intervals and increases towards the upper limits of IGT and IFG (ref.^{24,25}). The predictors of progression from prediabetes to T2DM include weight gain, the development/progression of insulin resistance (IR), decreased insulin secretion or an adverse adipocytokine profile²⁶.

Numerous studies have shown a drop in the incidence of progression from prediabetes to T2DM following both lifestyle and pharmacological measures. Among the pharmacological measures, metformin, acarbose, rosiglitazone and pioglitazone seem to be the most powerful drugs, as

evidenced by several randomized controlled trials²⁷. Some studies have also suggested a possible reverse process of transition from confirmed prediabetes to normal glucose levels due to the aforementioned measures¹⁷.

PREDIABETES AND INCREASED RISK OF OTHER DISEASES

Increased risk of cardiovascular disease (CVD)

In 2017, approximately 4 million people aged between 20 and 79 years were estimated to die of diabetes-related causes, with the greatest proportion of them dying of CVD (ref.¹⁸). The overall risk of CVD in diabetics is 2-4 times higher than in those without DM (ref.²⁸). However, the increased risk of CVD is already present at the prediabetes stage, as evidenced by numerous studies. The presence of prediabetes is estimated to increase the risk of CVD by approximately 20% as compared with healthy individuals²⁹, as confirmed by a large meta-analysis of prospective studies including more than a total of 1,600,000 participants which showed the relative risk (RR) of overall CVD morbidity to be 1.13 for isolated IFG (the ADA criteria), 1.26 for IFG (the WHO criteria) and 1.3 for IGT, and of all-cause mortality to be 1.13, 1.13 and 1.32, respectively³⁰. As in the risk of progression from prediabetes to T2DM, the risk of CVD increases towards the upper limits of IGT and IFG diagnostic cut-offs³¹. Some authors have even reported evidence of increased CVD risk as early as at the stage of normal glucose levels just below the prediabetes threshold³². A prospective study (n=10,913) showed increased risk of CVD morbidity of 1.53 (95 % CI 1.22-1.91) in individuals with FPG 5.3-5.5 mmol/L as compared with those with FPG 4.4 mmol/L (ref.³³).

Many studies consider IGT a stronger predictive factor for CVD morbidity and mortality than IFG. A large study composed of 10 European cohort studies confirmed the presence of IGT as an independent predictive factor for overall and CVD mortality. However, this was not true for IFG (the WHO criteria) alone³⁴. Similar findings were reported by the Hoorn Study in the Netherlands³⁵ and for CVD morbidity by the Framingham Offspring Study³⁶, a Finnish study by Lind et al.³⁷ or the Funagata study in Japan³⁸. By contrast, a meta-analysis by Ford et al. failed to show a difference in the predictive power of IFG (the WHO criteria) and IGT for the risk of CVD (ref.³⁹). In addition to IFG and IGT, there is relative agreement on the predictive power of increased HbA1c which seems to be at least the same as that of the two disorders, for relationships between this marker and both CVD morbidity^{40,41} and all-cause mortality⁴².

Macrovascular complications

A pathogenetically important role in the development of macrovascular complications in diabetics is played by acceleration of atherosclerotic changes in arteries⁴³. Today, however, reliable evidence is available on acceleration of this degenerative process at both molecular⁴⁴

and clinical levels⁴⁵ already at the prediabetes stage. In real practice, these degenerative processes are greatly contributed to by the concurrent presence of multiple risk factors, such as arterial hypertension, dyslipidemia, with mutually potentiating effects, very often accumulated in metabolic syndrome (MetS) (ref.⁴⁶). The relative importance of glucose metabolism disorders is likely to decrease with age, probably as a result of development of other cardiometabolic risk factors²⁹.

Coronary artery disease (CAD)

There are numerous studies showing a higher prevalence of prediabetes in patients with CAD and, moreover, some prospective studies show a higher risk of CAD in prediabetics. A meta-analysis of prospective cohort studies (n=527,021) revealed increased risks of CAD in participants with IFG defined both as the ADA or WHO criteria (RR 1.11, 95% CI 1.02–1.21; and RR 1.18, 95% CI 1.10–1.28, respectively) (ref.⁴⁷). Thus, not only prediabetes is likely to play a role in the development of CAD, but numerous studies have shown a poorer prognosis (higher reoccurrence and overall mortality rates) when compared with individuals without glucose metabolism disorders⁴⁸.

Stroke

The mean prevalence of prediabetes in patients with stroke or transient ischemic attack in the acute phase is 37%. The lowest and highest rates were 29% in China and 53% in the USA, respectively; once again, this is clearly higher than the prevalence of prediabetes in the general population¹². A large meta-analysis of cohort studies (n=760,925) found, after adjustment for common risk factors, an independent association between IGT, or combination of IFG (the ADA criteria) and IGT, and an increased risk of future stroke (RR 1.2, 95% CI 1.07–1.35) (ref.⁴⁹). Prediabetes, in particular the presence of IGT, is considered an independent risk factor for the development of stroke and a strong predictor of its recurrence by most studies¹². In addition to the increased risk of stroke, prediabetes is known to be linked to a poorer prognosis (worse neurological deficit) of patients following the event, as is the case of CAD (ref.⁵⁰).

Peripheral arterial disease (PAD)

Prediabetes is associated with a higher prevalence of PAD in comparison with individuals with no glucose metabolism disorder. An analysis of cross-sectional data of 3,607 US adults from the 1999–2004 NHANES revealed the lowest prevalence of PAD among persons with normal FPG (3.9%), higher among those with IFG (5.4%, the ADA criteria), and significantly higher among those with undiagnosed (9.2%) and diagnosed DM (7.5%) (ref.⁵¹).

Microvascular complications

In addition to the undoubted contribution of prediabetes to macrovascular complications, there have been discussions on its role in the development of long-term microvascular changes well-known in individuals with established DM, that is, retinopathy, nephropathy and neuropathy²⁶.

Retinopathy

While many studies have shown an association between prediabetes and retinopathy, their conclusions are rather varied, depending on the methods used⁵². Based on findings from the Diabetes Prevention Program, approximately 8% of prediabetics have clinical signs of retinopathy⁵³. As for the components of prediabetes, reliable evidence is only available for the association between retinopathy and IGT, as shown, after adjustment for common risk factors, by the Funagata study (odds ratio [OR] 1.63, 95% CI 1.07–2.49); the relationship between IFG (the WHO criteria) and retinopathy was not statistically significant⁵⁴. Even a large analysis of three cross-sectional studies by Wong et al. (n=11,423) failed to give evidence on a clear and consistent glycemic threshold under the DM cut-off for the presence of retinopathy across different populations⁵⁵. In their study of individuals without hypoglycemic medication, Cheng et al. reported HbA1c to discriminate prevalence of retinopathy better than FPG, with a marked increase in the prevalence of retinopathy for HbA1c values of 37 mmol/mol or more⁵⁶.

Nephropathy

The evidence is more convincing for the impact of prediabetes on the development of nephropathy. Studies have shown that up to one third of individuals suffer from chronic kidney disease (CKD) as early as at the time of DM diagnosis. A study of 6,453 adult Americans without DM revealed that the prevalence of CKD (glomerular filtration rate [GFR] below 60 mL/min/1.73 m² body surface area) increased from 1.2% of individuals with FPG between 4.9 and 5.3 mmol/L to 4% in those with FPG above 5.7 mmol/L (ref.⁵⁷). A meta-analysis of 8 cohort studies (n=185,452) suggests that the RR of developing CKD as defined above is 1.12 (95% CI 1.02–1.21) in persons with IFG (the ADA criteria) (ref.⁵⁸). Similarly, the NHANES (1999–2006) confirmed the higher prevalence of CKD in prediabetics (17.7%) as compared with those without glucose abnormalities (10.6%) (ref.⁵⁹). Glucose metabolism disorders have been shown to influence GFR. This was evidenced, for example, by the Framingham heart study in which individuals with prediabetes initially without CKD showed a GFR decreased by 9 mL/min/1.73 m² body surface area after 7 years⁶⁰. But once again, the effect of clustered risk factors contributing to CKD must be mentioned.

Many studies have suggested that the non-diabetic range of hyperglycemia is associated with an increased risk of albuminuria, which is considered the earliest marker of diabetic nephropathy. However, it is not clear what range of glucose levels, below that of DM, increases the prevalence of albuminuria. A Korean cross-sectional study (n=5,202) divided participants based on their FPG into 5 groups: < 5.0, 5.0–5.5, 5.6–6.0, 6.1–6.9, and ≥ 7.0 mmol/L. In these groups, the rates of albuminuria were 4.1%, 6.0%, 7.6%, 12.3%, and 23.4%, respectively, showing an increase in the prevalence of albuminuria not only between normal FPG and IFG, but also within the IFG range⁶¹.

Neuropathy

While peripheral neuropathy (PN) has traditionally been considered a late complication of DM, there has been increasing evidence on its association with prediabetes. Approximately 25-62% of individuals with idiopathic PN are reported to have prediabetes while 11-25% of prediabetics are thought to have PN and 13-21% have neuropathic pain⁶². As in some of the above consequences, there is evidence that the prevalence of PN has an increasing gradient, from normoglycemic persons to those with IFG and IGT to diabetics⁶³. The MONICA/KORA study including 195 diabetics and 198 controls classified according to their OGTT results revealed PN in 28% of diabetics, 13% of persons with IGT, 11.3% of individuals with IFG (the ADA criteria) and 7.4% of normoglycemic individuals. In the same cohort, neuropathic pain was found in 13.3% of diabetics, 8.7% of those with IGT, 4.2% of persons with IFG and 1.2% of individuals without glucose metabolism disorders⁶⁴. From a qualitative perspective, PN is milder in prediabetics, mainly associated with impaired sensitivity and only slightly impaired motor function⁶². Loss of plantar protective sensation and elevated mechanical stress are considered relevant factors in skin breakdown resulting in diabetic foot ulcerations. Prediabetic individuals seem to exhibit an altered plantar pressure distribution pattern similar to that often found in T2DM subjects⁶⁵.

Increased risk of cancer

Prediabetes is also associated with increased risk of cancer. Prediabetics are approximately 15% more likely to develop cancer (diabetics, 20-25%) than individuals with normal glucose levels and their mortality from cancer is higher by approximately 13% (ref.^{66,67}). Prediabetes and cancer have many common aspects and are linked both epidemiologically and biologically. They are characterized by delayed obvious clinical manifestations as well as similar risk factors such as age, nutrition, cigarette smoking and obesity. Possible pathogenic mechanisms linking prediabetes and T2DM with cancer include hyperglycemia (associated with increased oxidative stress), hyperinsulinemia (with its long-known mitosis-stimulating effect) and alterations in the insulin-like growth factor 1 (IGF-1) system, chronic subclinical inflammation, abnormalities in sex hormone metabolism (especially estrogens) and adipokines⁶⁸.

Epidemiologically, the effect of prediabetes on increased cancer risk has been shown for breast, pancreatic, colorectal, hepatic, endometrial and gastric tissues⁶⁸. The risk of developing breast cancer is approximately doubled by the presence of prediabetes, as seen from case-control studies by Crispo et al. (OR 1.94, 95% CI 1.32-2.87) or Salinas-Martínez et al. (OR 2.08, 95% CI 1.10-3.96) (ref.^{69,70}). A meta-analysis of five studies (n=576) showed a linear increase in the risk of pancreatic cancer by 13% (RR 1.13, 95% CI 1.08-1.19) for an increase in FPG by 1 mmol/L (ref.⁷¹). A large meta-analysis of prospective studies (n=4,462,151) also showed a significant linear association between fasting glucose levels and the risk of colorectal cancer. An increase in FPG by 1.11 mmol/L

was associated with an increase in the risk of colorectal cancer by 1.5% (RR 1.015, 95% CI 1.012-1.019) (ref.⁷²). A meta-analysis (n=1,384,594) by Xu et al. quantified an association between prediabetes and hepatocellular carcinoma (hazard ratio 1.21, 95% CI 1.13-1.30) (ref.⁷³). As compared with the above consequences of prediabetes, relatively little data are available on the relationship between prediabetes and cancer. Thus, further research is required that would provide valuable information, in particular for individuals having prediabetes for a long time without progression to T2DM.

PREDIABETES DETECTION

It is of paramount importance to perform regular preventive check-ups as these may aid in early detection of glucose metabolism disorders. Additionally, their results must not be underestimated. Waist circumference is an easily accessible parameter identifying individuals at a higher risk of glucose metabolism disorders as well as other components of MetS (ref.⁷⁴). Therefore, this parameter should be more emphasized in the screening. It would be desirable to add HbA1c analysis to routine screening for prediabetes globally as it would increase the sensitivity of prediabetes detection.

Along with the well-established measures of prediabetes, such as FPG and OGTT, new potential biomarkers need to be implemented into routine practice to become useful tools to aid in efforts for early prediabetes detection and treatment. Analysis of IR using noninvasive methods is highly desirable to be included in routine practice. The assessment of the level of IR using the Homeostatic Model Assessment (HOMA) has been repeatedly correlated with the insulin clamp method. A common use of the HOMA could help to detect the early onset of IR, which is generally considered to be a primary disorder leading to the development of other glucose metabolism disorders as well as other components of MetS. Also, adipokine analysis could find a clinical use in the near future. In this way, adiponectin and its high molecular weight (HMW) form appear to be potential biomarkers as hypoadiponectinemia plays an important causal role in the development of IR, T2DM and MetS. Moreover, serum levels of HMW adiponectin are independent of the feeding/fasting cycle⁷⁴. Analytical studies have confirmed the ability of the HOMA and adiponectin levels to predict the onset of glucose metabolism disorders⁷⁵. What is more, technical and economic difficulties of these biomarkers' analysis slowly lower, which could enable their incorporation into the routine practice. Fig. 2. depicts the development of glucose metabolism disorders in time with a special emphasis on their biomarkers.

SUMMARY

Prediabetes is a major challenge for both clinical and theoretical medicine. This condition not only leads to the development of T2DM in most cases but also contributes

Fig. 2. Basic summary of development of glucose metabolism disorders with their biomarkers. HOMA – homeostatic model assessment, FPG – fasting plasma glucose, OGTT – oral glucose tolerance test, HbA1c – hemoglobin A1c

to the onset of other complications. On the other side, it is a long-developing disorder which offers enough time for early diagnosis and intervention. There is still a lack of data on the prevalence of prediabetes in various parts of the world including the Czech Republic. It must be reminded that recent years have witnessed an increase in the prevalence of child obesity with manifestation of the first signs of metabolic disorders formerly seen mainly in adults (e.g. IR and arterial hypertension). Such children have been shown to be more likely to become obese in their adulthood, facing all the negative consequences including the impact of obesity on glucose metabolism⁷⁶.

The implementation of healthy lifestyle practices (regular exercise, balanced diet and avoiding cigarette smoking) has the greatest effect on preventing chronic non-infectious diseases including prediabetes. Adhering to the principles of a healthy lifestyle is a lifelong process that should address all individuals throughout the population, with systematic health education starting in childhood. Preventive measures can be classified into population-level (public health) and individual-level interventions. For individual interventions, it is critical to select an individual (or a group of individuals) to administer the particular personalized intervention according to an appropriate prediction of future CVD risk⁷⁷. From a perspective of primary care providers, prediabetes detection should be targeted to patients who are most likely to benefit from diagnosis and treatment. Improving access to lifestyle intervention programs and educating providers about evidence-based treatments for prediabetes and how to effectively discuss treatment options with patients may improve both providers' and patients' engagement in T2DM prevention⁷⁸.

From a clinical point of view, it is desirable to focus on the following factors: blood pressure, FPG, plasma lipids, platelet stabilization, cigarette smoking, physical activity, body weight and eating habits⁷⁹. In prediabetics, an emphasis on a complex control of these factors and their optimization contributes to a decrease of CVD risk and can also contribute to a regression of prediabetes.

In many countries, apart from non-pharmacological methods, metformin administration is recommended in prediabetics with at least another one present risk factor. A network of general practitioners cooperating closely with diabetologists and other specialists is the basis for detection and treatment of prediabetes⁸⁰. With the aforementioned growing prevalence, the care for prediabetics may become a domain of primary care workers more than diabetologists.

CONCLUSIONS AND FUTURE PROSPECTS

Many countries lack adequate population-representative data for estimating the prevalence of prediabetes. The presence of prediabetes means a higher risk of morbidity and mortality due to cardiovascular and oncological complications. There is reliable evidence of an increased risk of developing macrovascular as well as microvascular complications and some tumors in prediabetics. The extent of the risk as well as the numbers of studies supporting this vary depending on the particular complications. Thus, relatively few data are available on the relationship between prediabetes and cancer.

The unfavorable trends in the prevalence of prediabetes and T2DM worldwide require, in addition to a greater emphasis on their primary prevention, a greater focus not only on early detection of these two diagnoses but, ideally, to increase the effectiveness of possible interventions, on detection of metabolic disorders that precede both prediabetes and T2DM. Secondary prevention of these early disorders may be improved by adding the HOMA determination used for identifying individuals with IR to routine preventive examinations. Waist circumference and its predictive power also must not be underestimated.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies on the nosological entity of prediabetes, its definition, epidemiology and its role as a risk factor for other

health consequences. Scientific articles from 1974 to 2018 were searched using the PubMed and Web of Science databases and references from relevant articles using the terms “prediabetes”, “impaired fasting glucose”, “impaired glucose tolerance”, “definition”, “detection”, “epidemiology”, “prevalence”, “cardiovascular disease”, “atherosclerosis”, “coronary artery disease”, “stroke”, “peripheral arterial disease”, “retinopathy”, “chronic kidney disease”, “nephropathy”, “neuropathy” and “cancer”. All searches were up to date as of April 2018. Publications from the last 10 years were preferred.

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