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Review Article

Diagnosis and Management of Pre-Diabetes: A Systematic Review

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Abstract

The increasing incidence of diabetes is a major health issue The detection and management of prediabetes can delay the onset of diabetes. For that, we conducted a systematic electronic database search for relevant studies published from inception and till 30th May 2020 in seven databases. Finally, we included 47 studies in this systematic review. Screening for pre-diabetes should be considered in asymptomatic adults, at any age, with body mass index (BMI) ≥ 25 kg/m2 (Asian Americans: ≥ 23 kg/m2) with one or more of diabetes risk factors, women with gestational diabetes mellitus, and all patients aged ≥ 45 years. It should be also done in children and adolescents following the puberty onset or > 10 years of age, whichever earlier, if their BMI ≥ 85th percentile and have one or more of diabetes risk factors. The mainstay of lifestyle interventions is to adjust the modifiable risk factors such as increasing physical activity, promoting a healthy diet, and weight reduction. However, the health care workers showed substantial resistance to maintaining lifestyle counseling in the long term. Multiple treatment options have been tried in the context of prediabetes; including antidiabetics or non-antidiabetics; however, Metformin sounds to be the best candidate. In conclusion, an integrated system of pre-diabetes screening and management in different care settings is highly recommended.

Keywords: *Prediabetes; Screening; Lifestyle Intervention; Metformin*

Introduction

Pre-diabetes is used to describe a condition where patients have abnormal blood glucose that is not high enough to satisfy the criteria for diabetes [1]. This term refers to three biochemical abnormalities: high HbA1c, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [1,2]. It is estimated that 6.7% of the world's adult population (about 318 million individuals) have pre-diabetes [3]. This number is expected to increase to 470 million individuals by 2030 and 482 million individuals (7.8% of the world's adult population) by 2040 [3]. What makes these statistics alarming is the fact that about 70% of pre-diabetics would develop diabetes at some later stage of their lives [3,4]. Noteworthy, the individuals with both IGT and IFG have a doubled risk to develop diabetes compared to those having only one of them [3].

According to the U.S. Preventive Services Task Force, pre-diabetes screening is recommended, followed by referring positive individuals to a strict lifestyle intervention with a healthy diet and adequate physical activity [5,6]. Lifestyle modification and Metformin usage found to produce a durable (> 15 years) reduction of diabetes rates, among pre-diabetics, by 58% and 31%, respectively [7]. In addition,

those interventions found to minimize micro- and macrovascular diseases, cardiovascular-specific mortality, and all-cause mortality [7]. Nevertheless, similar interventions are not fully integrated into the routine prevention of diabetes [7]. Pharmacological treatment would be the next option when lifestyle modifications have failed; however, there no standard treatment for those individuals [8].

The progression of pre-diabetic individuals to diabetics is variable according to the patients' characteristics and the diagnostic criteria used [4,9]. The progression rate to diabetes is about 4%-6% and 6%-9% for isolated IGT and isolated IFG, respectively [10]. The incidence rate of diabetes, among prediabetics with HbA1c 6.0 - 6.4%, was 35.6 per 1,000 person-years [11]. However, lifestyle modification combined with metformin found to be effective in decreasing the relative risk of diabetes by 20% [12]. Moreover, these interventions were able to reduce the diabetes progression rate by 6% (4% versus 10%) at a one-year follow up and by 7% (14% versus 23%) at a three-year follow up [13]. The aforementioned data highlights the importance of identifying individuals with pre-diabetes and introducing the proper intervention to them. For that, we performed this systematic review to emphasize the importance of screening and treatment interventions among pre-diabetics.

Methods

Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review [14]. A systematic electronic database search was conducted for relevant studies published from inception and till 30th May 2020 in seven databases including Google Scholar, Scopus, Web of Science (ISI), PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and CINAHL using keywords, medical subject (MeSH) terms. In databases not supporting MeSH terms, combinations of all possible terms were used. Moreover, We conducted a manual search of references from the included articles by searching the primary studies that had cited our included papers and scanning references of the relevant papers in PubMed and Google Scholar to avoid missing any relevant publications [15].

We included the most appropriate (high quality/low risk of bias) published studies that diagnosis and management of pre-diabetes. Papers were excluded if there was one of the following exclusion criteria: non-human (*in vitro* or animal) studies, pilot studies, duplicate records, data could not be reliably extracted or incomplete reports, abstract only articles, thesis, books, conference papers. Moreover, studies discussing the perspectives of health care workers were excluded since the personal views are not the focus of the current study. title and abstract screening were done independently by four reviewers. Then, three independent reviewers performed a full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was resolved by discussion and referring to the senior author when necessary.

Data extraction

Two authors developed the data extraction sheet using the Microsoft Excel software. Data extraction was performed by three independent reviewers using the excel sheet. The fourth independent reviewer performed data checking to ensure the extracted data accuracy. All the disagreements and discrepancies were resolved by discussion and consultation with the senior author when necessary.

Quality assessment

Three independent reviewers evaluated the risk of bias in the included studies. The National Institutes of Health (NIH) quality assessment tools were used to determine the quality of included studies, according to their study design [16]. Any discrepancy between the reviewers was solved through discussion. This step was done only to assess the quality of the evidence to include only studies with fair to good quality (and exclude studies with poor quality), that is why no reporting of individual studies was provided.

Results and Discussion

Search results and summary of included studies

We identified 4,104 records after excluding of 857 duplicates using the Endnote X9 software. Title and abstract screening resulted in 119 records for further full-text screening. Two papers were added after performing manual search trials. Finally, we included 47 studies in this systematic review (Figure 1). Due to the large number of included studies, we provided a summary of the main studies in the literature (Table 1).

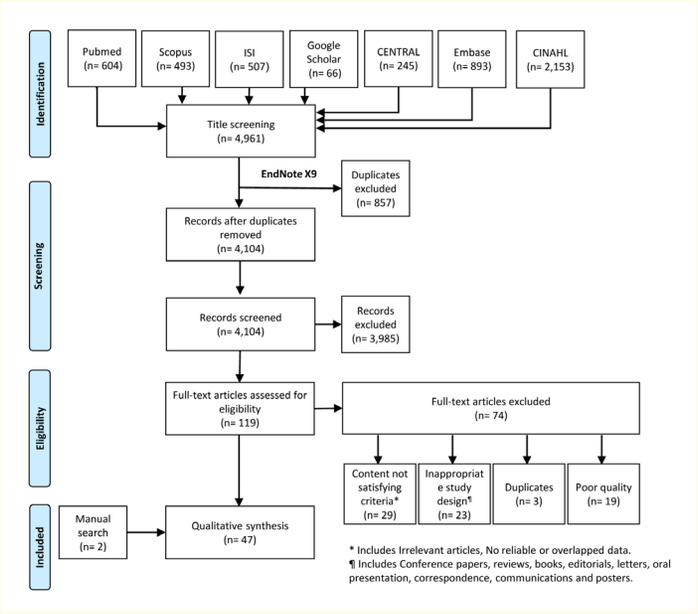

Figure 1: *PRISMA flowchart of search and screening process.*

Author, year	Country	Sample size	Male, %	Age, Mean (SD)	Objective	Main conclusion(s)
Al Amri, 2019 [17]	Saudi Arabia	613	45.2	32±11.8	To assess the association of prediabetes with lipid metabolism disorders to clarify whether systematic screening for prediabetes should be proposed for individuals with dyslipidemia.	Even though high LDL-C is associated with an increased probability of prediabetes, a recommendation for universal screening of dyslipidemic patients requires further cohort studies.
Bertram, 2010 [18]	Australia	six million	-	NA	to evaluate the cost-effectiveness of a screening program for pre-diabetes, which was followed up by treatment with pharmaceutical interventions or lifestyle interventions to prevent or slow the onset of diabetes in those at high risk.	Screening for pre-diabetes followed by diet and exercise, or metformin treatment is cost-effective and should be considered for incorporation into current practice. The number of dietitians and exercise physiologists needed to deliver such lifestyle change interventions will need to be increased to appropriately support the intervention.

Coppell, 2017 [19]	New Zealand	157	31.2	-	to examine the implementation and feasibility of a multilevel primary care nurse-led prediabetes lifestyle intervention compared with current practice on weight and glycated hemoglobin in patients with prediabetes, at 6 months.	Study findings confirm the feasibility and acceptability of primary care nurses providing structured dietary advice to patients with prediabetes in busy general practice settings. The small but potentially beneficial mean weight loss among the intervention group supports further investigation.
Costa-Pinel, 2018 [20]	Spain	1819	43.2	63.2 (8.0)	To describe both the preliminary results and barriers encountered along the first year of the implementation process.	The present results demonstrate that implementing a large-scale lifestyle intervention in primary healthcare is feasible and can be properly launched within a reasonably short time using existing public healthcare resources
Dawes, 2015 [21]	Canada	59	51	NA	To determine the feasibility of implementing a large-scale primary care-based diabetes prevention trial.	It is feasible to implement FLIP and to conduct a trial to assess effectiveness. A larger trial with longer follow up to assess progression to diabetes is warranted.
DeJesus, 2018 [22]	USA	53	-	NA	To assess the impact of individualized wellness coaching intervention for primary care patients with prediabetes on self-reported changes in physical activity level and food choices.	integration of wellness coaching in primary care practice among individuals at high risk for diabetes is feasible and may be useful as part of diabetes prevention management strategies in target populations.
Gu, 2015 [23]	New Zealand	28,192	-	48 (37-61)*	to investigate the incidence rate of prediabetes in NZ primary care.	EMR analysis identified an alarming incidence rate of prediabetes, especially among Māori and Pacific groups, highlighting the need to better prevent and manage the condition.
Hillmer, 2017 [24]	Canada	1916	29.5	58.1 (12.4)	evaluate the real-world effectiveness of the PCDPP, and to use a validated diabetes risk modeling tool to estimate the impact of scaling up the program	Primary Care Diabetes Prevention Program may represent a potentially effective tool for population-level diabetes risk reduction.
Hooks-Anderson, 2015 [25]	USA	3967	40.3	59.3 (13.6)	to determine whether there are any race-related disparities in the prevalence of provisions for diabetes education in primary care clinics for patients with diabetes and prediabetes.	Being African American independently increased the likelihood of referral for diabetes education in patients with prediabetes and patients with diabetes. After adjusting for patient comorbidities and risk factors, this association remained significant for patients with prediabetes. Additional research is needed to determine if provider beliefs and attitudes regarding race and diabetes education account for this association

Kolb, 2015 [26]	USA	54	18.5	NA	This study assessed the baseline knowledge, perceptions, attitudes, and behaviors of prediabetes patients to tailor a new technology-enhanced primary care-based lifestyle modification intervention.	Participants in this sample demonstrated requisite levels of knowledge, self-efficacy, motivation, and risk perception for effective behavior change. These data suggest that primary care-based prediabetes interventions can move beyond educational goals and focus on enhancing patients' ability to select, plan, and enact action plans.
Liddy, 2013 [27]	Canada	74	-	NA	We examined the feasibility of implementing a pre-diabetes program into a primary care clinic in Ottawa, Canada.	The translation and implementation of research evidence into clinical practice is complex and requires consideration of real-life practicalities such as time demands on participants, staffing costs, effective recruiting, and ongoing evaluation.
Lim, 2019 [28]	Singapore	423	52.3	NA	to assess factors associated with fulfilling the healthy plate recommendation, and to explore reasons for the behavior among primary care patients with prediabetes in Singapore.	Apart from the individual and interpersonal levels, practitioners and policy makers need to work together to address the organisational, community and policy barriers to healthy eating.
Lim, 2020 [29]	Singapore	433	51.3	NA	to assess factors associated with meeting the recommendation of at least 150 min of moderate/vigorous physical activity weekly, and to explore facilitators and barriers related to the behaviour among primary care patients with prediabetes in Singapore.	Much more remains to be done to promote physical activity among primary care patients with prediabetes in Singapore. Participants reported facilitators and barriers to physical activity at different levels of the SEM. Apart from the individual and interpersonal levels, practitioners and policy makers need to work together to address the organisational, community and policy barriers to physical activity.
Linmans, 2011 [30]	Netherlands	2818	44.1	66.7 (12.55)	The aim of our study was to investigate the effectiveness of the Dutch lifestyle programme for patients with diabetes or prediabetes in real-world primary care setting, using regular medical registration to evaluate the observed effects.	The effects of the lifestyle programme in real-world primary care for patients with prediabetes or T2DM were small and not statistically significant. The attention of governments for lifestyle interventions is important, but from the available literature and the results of this study, it must be concluded that improving lifestyle in real-world primary care is still challenging.
Mainous, 2016 [31]	USA	518	53.3	NA	To decide whether primary care physicians diagnose prediabetes and adjust the treatment plan in light of HbA1c results	Our findings show that there are missed opportunities for diabetes prevention in primary care. Providers need to change their approach to prediabetes and play a more effective role in preventing diabetes.

Neumann, 2017 [32]	Sweden	-	-	NA	To estimate the cost-effectiveness of a T2D prevention initiative targeting weight reduction, increased physical activity and a healthier diet in persons in pre-diabetic states by comparing a hypothetical intervention versus no intervention in a Swedish setting.	The prevention or the delay of the onset of T2D is feasible and cost-effective. A small investment in a healthy lifestyle with change in physical activity and diet together with weight loss are very likely to be cost-effective.
Rossen, 2015 [33]	Sweden	310	-	NA	The aim of this paper is to describe the design and recruitment procedure, methods, and the theoretical framework for the physical activity promotion program Sophia Step Study.	This study will show if a multi-component intervention using pedometers with group- and individual consultations is more effective than a single- component intervention using pedometers alone, in increasing physical activity and improving HbA1c, other metabolic and cardiovascular risk factors, physical activity levels and overall health in patients with pre- and type 2 diabetes.
Sherman, 2017 [34]	USA	17	59	52 (12.44)	To assess if the use of a health coaching intervention among primary care patients, with prediabetes, warrants further examination	A health coaching intervention used among primary care patients, with prediabetes, deserves further examination, as participants had a significant reduction in hemoglobin A1c and weight over 2 years
Sohler, 2016 [35]	USA	11885	38.4	48.57 (17.5)	To describe the use of HbA1c testing for screening during routine visits in primary care clinics of an urban health care system in the U.S	In urban primary care settings, appropriate HbA1c testing could result in the detection of a substantial number of previously undiagnosed diabetes and prediabetes cases needing treatment.
Weir, 2014 [36]	Canada	45	35.6	58.6 (8.2)	to describe the results of a single 3 h pre-diabetes patient education programme provided by the St. Albert and Sturgeon Primary Care Network in Alberta, Canada	A “one-off”, theory-guided group education session may be insufficient to support lifestyle modifications in the context of weight management in a pre-diabetic population.
Young, 2019 [37]	USA	67	NA	NA	The primary aims were to pilot study elements, including identification of eligible patients; health care provider recruitment, training, and engagement; patient recruitment; data collection procedures; and a 24-week intervention	If a fully powered trial is successful, primary care settings with “behind-the-scenes” information technology support may be appropriate to increase physical activity among patients with prediabetes and diabetes

Table 1: *Summary of the main included studies discussing pre-diabetes.*

*NA: Neither mean nor median were provided; *: Median and interquartile range.*

Diagnosis of pre-diabetes

Screening of pre-diabetes

Screening for pre-diabetes should be considered in asymptomatic adults, at any age, with body mass index (BMI) ≥ 25 kg/m^2 (Asian Americans: ≥ 23 kg/m^2) with one or more of diabetes risk factors, women with gestational diabetes mellitus and all patients aged ≥ 45 years [1]. It should be also done in children and adolescents following the puberty onset or > 10 years of age, whichever earlier, if their BMI ≥ 85th percentile and have one or more of diabetes risk factors (Table 2) [1,38].

A) Criteria for testing for diabetes or prediabetes in asymptomatic adults
1. Testing should be considered in overweight or obese (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors: • First-degree relative with diabetes. • High-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander). • History of CVD. • Hypertension (≥ 140/90 mmHg or on therapy for hypertension) • HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L). • Women with polycystic ovary syndrome • Physical inactivity. • Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. Patients with prediabetes (A1C ≥ 5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting
B) Criteria for testing for diabetes or prediabetes in asymptomatic, adolescents and children
- Testing should be considered in youth* who have overweight (≥ 85th percentile) or obesity (≥95th percentile) A and who have one or more additional risk factors based on the strength of their association with diabetes:
• Maternal history of diabetes or GDM during the child's gestation.
• Family history of type 2 diabetes in first- or second-degree relative.
• Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander).
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight).

Table 2: *Risk-based screening for prediabetes/diabetes in adults, adolescents, and children [1,38].*

*CVD: Cardiovascular Disease; GDM: Gestational Diabetes Mellitus; * After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals, or more frequently if BMI is increasing, is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.*

In a retrospective review of adults aged ≥ 45 years visiting primary care setting, 33.6% of the patients had pre-diabetes, based on their HbA1v values [31]. In the same study, the diagnosis was very low among patients with HbA1c consistent with pre-diabetes [31]. Another retrospective analysis of 2-year records showed that appropriate HbA1c could be used as an appropriate screening tool to detect a considerable number of undiagnosed prediabetes or diabetes [35]. It found that about 10% of the patients had HbA1c levels in the diabetes range and about half of them had levels in the prediabetes range [35]. Using the HbA1c as a screening tool in 28,192 adults in primary care, the prediabetes incidence was 5%, highlighting the need for a proper screening plan to prevent progression to diabetes [23].

In a Saudi study of 613 attendants of primary care health centers, 28.7% were identified as pre-diabetics and 54.2% had dyslipidemia [17]. Moreover, there was an association between prediabetes and high low-density lipoprotein-cholesterol levels [17]. This highlights the need for screening for pre-diabetes among dyslipidemic patients [17].

Pre-diabetes diagnostic criteria

As mentioned before, patients will be diagnosed with pre-diabetes if they have IGT and/or IFG and/or HbA1c = 5.7 - 6.4% [1]. IFG would describe fasting plasma glucose levels between 100 and 125 mg/dL, and IGT is defined as 2-h plasma glucose levels, during a 75-g oral glucose tolerance test, between 140 and 199 mg/dL [39-41] (Table 3).

Criteria defining prediabetes *
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)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

Table 3: *Criteria for diagnosing pre-diabetes.*

*FPG: Fasting Plasma Glucose; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; OGTT: Oral Glucose Tolerance Test; 2-h PG: 2-h Plasma Glucose; * 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.*

Similar to glucose measures, HbA1c showed a strong predictive value regarding the progression of diabetes. A 5-year incidence of diabetes was 9 - 25% and 25 - 50% in patients with HbA1c of 5.5 - 6.0% and 6.0 - 6.5%, respectively [42]. The latter group has a 20-time higher risk of developing diabetes compared to those with HbA1c of 5.0% [42]. Compared to the fasting plasma glucose, HbA1c showed a better performance in predicting the risk of subsequent diabetes and cardiovascular disease [43].

Management of pre-diabetes

Lifestyle interventions

The mainstay of lifestyle interventions is to adjust the modifiable risk factors such as increasing physical activity, promoting a healthy diet, and weight reduction [44]. The two largest lifestyle interventions to prevent diabetes are the Finnish Diabetes Prevention Study (DPS) and the US Diabetes Prevention Program (DPP); have both shown the beneficial effect of these interventions [45,46]. In the DPP study, the incidence of diabetes in the lifestyle intervention group was 4.8 cases/100 person-years, compared to 11 and 7.8 cases/100 person-years in placebo and metformin groups, respectively [46]. The lifestyle modification group caused a decline incidence rate by 58% compared to 31% in the Metformin group [46]. Similarly, in the DPS, lifestyle changes successfully reduced the diabetes incidence by 58%, with a cumulative incidence of 11% compared to 23% in the control group [45]. A summary of the administered lifestyle interventions is presented in table 4.

Author, year	Country	Intervention	Results
Coppell, 2017 [19]	New Zealand	The intervention primary care and community education nurses participated in a 6-h theoretical and practical training course, which included nutrition principles, dietary assessment, goal setting, the context within which nutrition advice is given and how to measure height, weight and waist circumference	the intervention group lost a mean 1.3 kg more than the control group ($p < 0.001$). Mean HbA1c, BMI and waist circumference decreased in the intervention group and increased in the control group, but differences were not statistically significant. Implementation fidelity was high, and it was feasible to implement the intervention in busy general practice settings
Dawes, 2015 [21]	Canada	The FLIP program was designed following a review of current evidence and was informed by focus groups that included local family physicians. FLIP consisted of 3 elements: 1) lifestyle prescription; 2) a pedometer; and 3) support by a community based facilitator for 6 months.	Adherence to the intervention was high (97%), with 34 of 35 patients continuing to receive telephone calls from the facilitator for 6 months. The mean cost of the intervention was C$144 per person. Compared with control, intervention participants significantly reduced weight by 3.2 kg (95%CI,1.7 to 4.6); body mass index by 1.2 (95% CI, 0.7 to 1.7) and waist circumference by 3 cm (95% CI, 0.3 to 5.7).
DeJesus, 2018 [22]	USA	The wellness coaching program consisted of 12 sessions which were completed within 16 weeks and were conducted at the participants' primary clinic site	Effect was sustained at 24 weeks. Success in making healthy eating choices also statistically improved from baseline. Significant effects on both activity level and eating behavior persisted even after adjusting for age, sex and baseline glucose/A1c values. Secondary outcomes of self-efficacy and quality of life likewise showed significant improvement.
Hillmer, 2017 [24]	Canada	the programs aims to achieve a 7% weight loss, engage in ≥150 minutes/week of moderate physical activity, and increase and retain knowledge about healthy lifestyle practices.	Weight loss over 9 months was 7.5% (or 6.8 kg), with 7.4% (or 6.4 kg) in females and 8.6% (or 8.6 kg) in males. When modeled, changes in weight were all statistically significant. The models for male participants predicted, however, some gains in weight in the last 3 months of the program. Dropout rates were 26.8%, 46.8% and 63.0% at 3rd, 6th and 9th month respectively. Scaling up the program would produce an NNT of approximately 36 and would avert 6401 cases of diabetes in five years.
Hooks-Anderson, 2015 [25]	USA	Patients were coded as having been referred to diabetes education if they had 1 or more of the following institution-specific referral orders placed: referral to dietitian, referral to family and community medicine clinical pharmacist, or referral to diabetic education	a significantly higher prevalence of African American patients with prediabetes were referred to diabetes education, and this association was also observed in patients with diabetes. In fully adjusted models, white patients with prediabetes were significantly less likely to be referred.
Kolb, 2015 [26]	USA	the ADAPT system uses the electronic medical record, pedometers and the internet to embed prediabetes-specific action planning into primary care encounters	Participants exhibited high risk of diabetes knowledge (knowledge score 20 on a 32-point scale) and high levels of willingness to make changes to decrease diabetes risk. Number of daily steps was inversely correlated with perceived physical activity ($r=-0.35082$, $p<0.001$). Poorer scores on diet quality were inversely correlated with BMI.

Liddy, 2013 [27]	Canada	"An Ounce of Prevention" consists of a session with series of 4 weekly group classes (2 hours each) and was offered to eligible individuals.	Results of the evaluation surveys show that participants are highly satisfied with the content as well as the format of the program and think that the content is relevant to them. Recruitment of patients is time- intensive and requires dedicated resources. Evaluation of effectiveness with follow-up surveys and clinical measures has been challenging due to limited resources and is ongoing.
Linmans, 2011 [30]	Netherlands	Within this nationwide lifestyle programme, patients have regular checks annually with their GP and quarterly (three times per year) with a diabetes practice nurse (DPN) and if necessary in between. Every patient receives lifestyle advice from the DPN. Patients go to a dietician for a consultation on nutritional advice when they are diagnosed with the disease and if they start insulin therapy.	There was no significant difference at follow-up in any outcome measure between either group. The reduction at one year follow-up of HbA1c and fasting glucose was positive in the intervention group compared with controls, although not statistically significant
Rossen, 2015 [33]	Sweden	Group A participants are offered 12 group meetings over two years' time, with the majority of meetings being held in the first six months. The group meetings include a 30 min walk and 60 min group consulting and are steered by a health professional trained in physical activity promotion and familiar with models and techniques for behavior change.	Measurements are made at week 0, 8, 12, 16, month 6, 9, 12, 18 and 24, including metabolic and cardiovascular biomarkers (HbA1c as primary health outcome), accelerometry and daily steps. Furthermore, questionnaires were used to evaluate dietary intake, physical activity, perceived ability to perform physical activity, perceived support for being active, quality of life, anxiety, depression, well-being, perceived treatment, perceived stress and diabetes self- efficacy.
Sherman, 2017 [34]	USA	Patients who enrolled in health coaching agreed to participate for at least 12 weeks with the APF's health coach	A health coaching intervention used among primary care patients, with prediabetes, deserves further examination, as participants had a significant reduction in hemoglobin A1c and weight over 2 years
Weir, 2014 [36]	Canada	session was developed in partnership with Alberta Health Services with the goal of preventing or delaying type 2 diabetes in pre-diabetic patients through targeting a 5–10% reduction in body weight by limiting dietary fat and increasing dietary fibre consumption, as well as increasing physical activity levels to 30 min, 5 times per week. These	we observed general trends towards improvements in diet, physical activity and weight related behaviours among the 45 completers, no significant changes were observed among participants between questionnaire periods.
Young, 2019 [37]	USA	telephone counseling, using motivational interviewing (MI) and individualized support, to assist participants in increasing and maintaining their physical activity.	Psychosocial measures significantly improved in four of the five factors for physical activity motivation relative to participants in the usual care arm. The more internally focused factors for exercise self-regulation and outcome expectancies scores were significantly greater for participants in intervention compared with usual care. Moderate to vigorous physical activity improved in intervention participants relative to usual care, but the difference was not statistically significant. No adverse events were noted.

Table 4: *Summary of the major administered lifestyle interventions.*

A large-scale study of 103 primary care centers, covering 1.4 million inhabitants, showed that lifestyle interventions can be properly implemented in primary care using the existing resources [20]. However, about 20% of the centers and one-third of the primary care workers showed substantial resistance to maintaining the initial effort or performing extra activities [20]. It seems that there is a defect in the referral system of pre-diabetics to lifestyle-changing interventions. In patients aged ≥ 45 years and have HbA1c level consistent with diabetes, only 23% were referred to lifestyle modification counseling and/or metformin [31]. In terms of cost-effectiveness, a combination of diet and exercise found to be the most cost-effective intervention, followed by Metformin intervention [18,32].

Pharmacological treatment

Multiple treatment options have been tried in the context of prediabetes; including antidiabetics (e.g. GLP-1 analogies, Thiazolidinediones, Biguanides, and α-Glucosidase Inhibitors) or non-antidiabetics [44]. Patients with IGT showed a 45% reduction in the risk of diabetes when treated with Metformin. Moreover, Metformin found to be as effective as lifestyle modification interventions in the Indian DPP and found to be more effective in patients with higher BMI and FPG [46,47]. Furthermore, the present evidence shows a slight advantage of Metformin, over lifestyle interventions, in the reduction of BMI, especially in the short term [48]. Table 5 shows a summary of the main trials of non-Metformin pharmacotherapy.

Author, year	Drug	Highlights
Chiasson, 2002/2003 [49; 50]	Acarbose	Acarbose was found to decrease the relative risk for diabetes by 25% among subjects with IGT during a 3.3 years of follow-up. The medication was associated with several gastrointestinal side effects such as flatulence and diarrhea and 31% of the participants in the acarbose arm dropped out before completion of the study.
Rosenstock, 2010 [51] and Astrup, 2012 [52]	Exenatide and Liraglutide	Exenatide and liraglutide have been demonstrated to have long term efficacy for sustained weight loss in obese subjects and reduce prevalence of prediabetes over a follow-up period of 1-2 years. The most common side effects with these drugs are nausea and vomiting and they remain injectable preparations.
Heymsfield, 2000 [53]	Orlistat	Over a 1.5 year follow-up period, use of Orlistat in conjunction with low energy diet is associated with greater weight loss as compared to placebo (6.7 kg vs 3.8 kg) and a decrease in conversion rate from IGT to overt diabetes (7.6% vs 3.0%) in obese adults
Torgerson, 2004 [54]	Orlistat	A 37% relative risk reduction in development of diabetes after 4 years of treatment
DeFronzo, 2011 [55]	Pioglitazon	Pioglitazone was found to decrease the risk of diabetes by > 70% in obese subjects with IGT in the ACT NOW study. Some of the added benefits were, decrease in diastolic blood pressure, reduction in rate of carotid intima-media thickness and a greater increase in HDL cholesterol but it was associated with increased weight gain (approximately 3 kg more than placebo) and edema (13% vs 6% in controls)
Ramachandran, 2009 [56]	Pioglitazon	There was no difference in incidence of diabetes between subjects receiving lifestyle intervention and placebo and subjects receiving lifestyle intervention and pioglitazone.
Dagenais, 2006/2008 [57; 58]	Rosiglitazone	Rosiglitazone was found to be effective in decreasing incidence risk of diabetes by 60% over a 3 year period but was associated with significant side effects such as an additional average weight of 2.2 kg in intervention group compared to controls and a higher incidence of heart failure (0.5% vs 0.1%) and total cardiovascular events (2.9% vs 2.1%).
Zinman, 2010 [59]	Rosiglitazone + Metformin (low doses)	Incident diabetes occurred in significantly fewer individuals in the active treatment group (14%) than in the placebo group (39%). The relative risk reduction was 66% and the absolute risk reduction was 26%, and 80% subjects in the treatment group reverted to normoglycemia compared to 53% in the control group, but the subjects in active treatment group had increased reports of diarrhea (16% vs 6% in controls).
Kawamori, 2009 [60]	Voglibose	A 40% risk reduction in incidence of diabetes in high-risk individuals with IGT with voglibose over a 48 wk period. Voglibose was noted to have a similar side effect profile as acarbose but only 7% subjects discontinued the use of drug due to adverse effects.

Table 5: *Summary of main trials of non-Metformin pharmacotherapy [44].*

IGT: Impaired Glucose Tolerance.

Conclusion

Risk-based screening for pre-diabetes is very important and the literature shows some shortcomings in this regard that need to be addressed. Lifestyle interventions with/without metformin are effective in reducing the risk of diabetes and maybe even superior to pharmacological treatment. An integrated system of pre-diabetes screening and management is highly recommended.

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No conflicts related to this work.

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Volume 5 Issue 8 August 2020