

Clinical Practice Guidelines

Prevention or Delay of Type 2 Diabetes Mellitus

2024



Clinical Practice Guidelines: Prevention or Delay of Type 2 Diabetes Mellitus

Acknowledgement:

We would like to acknowledge the Diabetes and Endocrinology Scientific Committee for adapting these guidelines.

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Abbreviations

BMI

Body Mass Index

CVD

Cardiovascular disease

DASH diet

Dietary Approach to Stop Hypertension

DPP

Diabetes Prevention Program

GRADE

Grading of Recommendations, Assessment, Development and Evaluation

HbA1c

Glycated hemoglobin A1c

RCT

Randomized controlled trial

Glossary

Cardiovascular diseases (CVDs)

A group of disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular disease and peripheral arterial disease.

HbA1c

Haemoglobin that is glycated by non-enzymatic attachment of glucose to haemoglobin. The concentration of HbA1c is the most commonly used measure of chronic glycaemia in clinical trials and diabetes management. It is used to reflect the integrated mean glucose level over the previous 8–12 weeks.

Metformin

A biguanide oral hypoglycemic agent used in treating type 2 diabetes. Complex mechanism of action. It decreases glucose production by the liver and enhances insulin sensitivity, opposes anti-inflammatory and anti-oxidant effects.

Prediabetes:

Prediabetes is a serious health condition where blood sugar levels are higher than normal, but not high enough yet to be diagnosed as type 2 diabetes.

Type 2 diabetes

A metabolic disease characterized by hyperglycemia, resulting from a defect in insulin secretion, insulin action or both. Long-term hyperglycemia is associated with micro and macrovascular complications.

Executive Summary

The prevalence of diabetes is globally increasing with a high incidence of complications. Targeted interventions and support are important in this high-risk group. Globally, more than 570 million adults live with diabetes so Prevention or delay of type 2 diabetes Mellitus (T2DM) is of great importance.

This guideline offers evidence-based recommendations for the prevention of diabetes. The recommendations are intended to provide healthcare professionals with practical guidance on preventing or delaying diabetes and associated co-morbidities improving healthy lifestyles for people with high risk of type 2 diabetes.

Recommendations

- Refer adults with overweight/obesity at high risk of type 2 diabetes, to an intensive lifestyle behavior change program for a weight reduction of at least 7% of initial body weight through a healthy reduced-calorie diet and 150 min/week of moderate-intensity physical activity. (**Strong recommendation**).
- A variety of eating patterns should be considered to prevent diabetes in individuals with prediabetes. Including Mediterranean diet, low carbohydrate eating plan, low fat, DASH diet (Dietary approaches to stop hypertension) (**Strong recommendation**)
- Prescribe metformin for prevention of T2DM in adult individuals with prediabetes, 25-59 years, those with high BMI ≥ 35 kg/m², higher fasting plasma glucose 100 - 125 mg/dL, higher HbA1C 5.7 – 6.4%, women with prior GDM (**strong recommendation**)
- Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease should be considered. (**Strong recommendation**)
- More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 100 –125 mg/dL, 2-h postprandial glucose 140 – 199 mg/dL, A1C 5.7 – 6.4%), and individuals with a history of gestational diabetes mellitus (**strong recommendation**)
- Pharmacotherapy should be considered to achieve sustained weight loss, minimize the progression of hyperglycemia, and cardiovascular risk reduction. (**strong recommendation**)

Introduction

The prevalence of T2DM is rapidly increasing with substantial personal and economic burden. Delay and prevention of diabetes is considered an important target for various interventions including lifestyle modification which has proven effective in preventing incident diabetes in high risk groups.

Various medications can also prevent or delay diabetes, whether diabetes prevention strategies also ultimately prevent the development of diabetic vascular complications are unknown, but cardiovascular risk factors are favorably affected.

Wide spread application has however been limited by local financial considerations.

Scope and purpose

The purpose of the work is to identify the best clinical practice guidelines in the prevention and delay of diabetes and to create actionable recommendations for healthcare professionals, adults with T2DM, and their families.

The objectives of these guidelines are

- To guide the proper program regarding lifestyle behavior change for diabetes prevention
- To consider the use of metformin therapy that should be used in adults at high risk for the development of diabetes.

Target audience

This guideline targets, healthcare professionals (internists, endocrinologists, family medicine physicians), dieticians, researchers, policymakers, public health practitioners, national diabetes programme managers, as well as non-governmental organizations (NGO).

Methodology:

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

Inclusion/ exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence)
- Selecting only national and/or international guidelines
- Specific range of dates for publication (using Guidelines published or updated in 2015 and later)

- Selecting peer reviewed publications only
- Selecting guidelines written in English language
- Excluding guidelines written by a single author, not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations

The following characteristics of the retrieved guidelines were summarized in a table:

- Developing organisation/authors
- Date of publication, posting, and release
- Country/language of publication
- Date of posting and/or release
- Dates of the search used by the source guideline developers

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members. The panel decided on a cut-off point or ranked the guidelines (any guideline scoring above 50% on the rigor dimension was retained). The GDG decided to adapt the American Diabetes Association – Standards of Care in Diabetes – 2024.

Evidence assessment

According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed GRADE information is available on the following sites:

- GRADE working group: <http://www.gradeworkinggroup.org>
- GRADE online training modules: <http://cebgrade.mcmaster.ca/>
- GRADE profile software: <http://ims.cochrane.org/revman/gradepro>

Table 1 Quality and Significance of the four levels of evidence in GRADE:

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 2 Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors above or if local adaptation has to account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations

Recommendation

a-Refer adults with overweight/obesity at high risk of type 2 diabetes, to an intensive lifestyle behavior change program for a weight reduction of at least 7% of initial body weight through a healthy reduced-calorie diet and 150 min/week of moderate intensity physical activity. (Strong recommendation, high certainty evidence)

Summary of evidence

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial¹, the Finnish Diabetes Prevention Study (DPS)², and the Da Qing Diabetes Prevention Study (Da Qing study)³, demonstrate that lifestyle/ behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardio-metabolic markers (such as blood pressure, lipids, and inflammation)⁴.

The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial¹. The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed a sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years

in the Da Qing study⁵, 43% reduction at 7 years in the Finnish DPS², and 34% reduction at 10 years⁶ and 27% reduction at 15 years⁷ in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking.

The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals⁸. Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44%⁹.

Rationale for the recommendation

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve $\geq 7\%$ weight loss during the first 6 months of the intervention. Further analysis suggests maximal prevention of diabetes with at least 7–10% weight loss⁹.

The goal for physical activity was selected to approximate at least 700 kcal/ week expenditure from physical activity. For ease of translation, this goal was described as at least 150 mins of moderate intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal⁸.

Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels^{10,11}. The preventive effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM)¹².

b. Lifestyle modifications: Intensive lifestyle modifications can reduce the incidence of T2DM. Lifestyle modifications include a healthy diet, increased physical activity, and encouraged weight loss for overweight or obese individuals.

c. Body weight management and physical activity Recommendations Refer Individuals with prediabetes to an intensive behavioral lifestyle intervention program with a target to achieve and

maintain a 7% loss of their initial body weight. Increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.

Recommendations

b-A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes, including Mediterranean diet, low carbohydrate eating plan, low fat, DASH diet (Dietary approaches to stop hypertension) (Strong recommendation, moderate certainty evidence)

Remarks

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories^{1,8,9}. However, evidence suggests that there are not an ideal percentage of calories from carbohydrates, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals¹⁰. Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages habitually consumed^{13,14} may also be appropriate for individuals with prediabetes¹³

Summary of evidence

Mediterranean-style and low-carbohydrate eating plans (high in vegetables, fruits, whole grains, beans, nuts and seeds, and olive oil) .^{15,16,17,18}. Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes^{19, 20,21,22}. Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes^{21, 23, 24, 25}. Individualized medical nutrition therapy is effective in lowering A1C in individuals diagnosed with prediabetes²⁶.

Recommendation

c-Pharmacologic Interventions: Prescribe metformin for prevention of T2DM in adult individuals with prediabetes, 25-59 years, those with high BMI ≥ 35 kg/m², higher fasting plasma glucose 100 – 125 mg/dL, higher A1C 5.7 – 6.4%, women with prior GDM. (strong recommendation, high certainty evidence)

Remarks

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for a specific indication of type 2 diabetes prevention. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost, side effects, and efficacy considerations. Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention²⁷.

Summary of evidence

weight loss through behavior changes in diet and physical activity alone can be difficult to maintain long term⁶, people at high risk of diabetes may benefit from support and additional pharmacotherapeutics options Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPPOS⁷, and metformin may be cost-saving over 10 years²⁸. In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥ 35 kg/m² and in younger participants aged 25–44 years¹. In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk²⁹. Both interventions remained highly effective during a 10-year follow-up period³⁰.

By the time of the 15-year follow up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥ 110 mg/dL vs. 95–109 mg/dL), those with a higher A1C (6.0–6.4% vs. $< 6.0\%$), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that benefitted the most from metformin³¹. In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP³². Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM or those with BMI ≥ 35 kg/m²). Consider periodic monitoring of vitamin B12 levels in those taking metformin chronically to check for possible deficiency^{33,34}.

Recommendation

d-Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. (Strong recommendation, moderate certainty evidence)

Remarks

In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs

to be balanced with the increased risk of weight gain, edema, and fracture. A lower dose may mitigate the risk of adverse effects.

Summary of evidence

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia³⁵, and are at increased risk for cardiovascular disease^{36,37}. If indicated, evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes.

In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study^{7,38}.

The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up^{3,5}. Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular disease risk factors³⁹. Statins have been associated with a modestly increased risk of diabetes^{40, 41, 42, 43, 44}. In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [95% CI] for incident diabetes 1.36 [1.17–1.58])⁴². In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes^{45, 46}.

In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes^{45,46}, suggesting a favorable benefit to harm balance with statin therapy.

Recommendation

e-More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 100–125 mg/dL, 2-h postprandial glucose 140–199 mg/dL, A1C 5.7–6.4%), and individuals with a history of gestational diabetes mellitus. (Strongly recommendation, high certainty evidence)

f-Pharmacotherapy should be considered to achieve sustained weight loss, minimize the progression of hyperglycemia, and cardiovascular risk reduction. (strong recommendation, moderate certainty evidence)

Remark

It is important to individualize the risk/benefit of intervention and consider person-centered goals. Risk models have explored risk-based benefit, generally finding the higher benefit of the intervention in those at highest risk⁹.

Summary of evidence

Individualized risk/benefit should be considered in screening, intervention, and monitoring to prevent or delay type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and the lifetime risk of complications^{47,48}. In the DPP, which enrolled high-risk individuals with impaired glucose tolerance, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo arm was 11.0 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 28.9%¹. Characteristics of individuals in the DPP/ DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases/100 person years) included BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, and A1C $\geq 6.0\%$), and individuals with a history of gestational diabetes^{1,29,30}. In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of older adults (mean age 75 years) with laboratory evidence of prediabetes (based on A1C 5.7–6.4% and/or fasting glucose 100–125 mg/dL), but not meeting specific BMI criteria, found much lower progression to diabetes over 6 years: 9% of those with A1C defined prediabetes, 8% with impaired fasting glucose⁴⁸.

Implementation considerations

Several barriers may hinder the effective implementation and scale-up of the recommendations in this guideline. These factors may be related to the behaviours of patients (or families), the behavior of healthcare professionals, the organization of care, health service delivery or financial arrangements.

Obstacles to effective implementation include:

- Patient engagement
- Collaboration; person centered, team based collaboration between clinician, dietitian, pharmacist and others involved in care delivery
- Behavior changes: information, guidance and support delivered easily and consistently can help assess sustained behavioral changes.

- Increase Awareness through educational programs development of prediabetes educational program is recommended and should be encouraged by different healthcare sectors which may include, but not limited to, awareness days, social campaigns, and printed materials.

Research needs

During the review of evidence and the development of recommendations, several research gaps were identified regarding the Egyptian population considered as a limitation of the body of evidence. Addressing these will help inform the revision of these guidelines.

1. **Tailoring Interventions:** Investigate the effectiveness of personalized or tailored interventions within diabetes prevention programs. Explore how individual characteristics, cultural factors, socioeconomic status, and health literacy influence program outcomes and identify strategies for optimizing intervention customization.
2. **Technology-Based Approaches:** Evaluate the effectiveness of technology-based interventions, such as mobile applications, wearable devices, and telehealth platforms, in enhancing diabetes prevention efforts. Assess the feasibility, acceptability, and impact of these technologies on participant engagement, behavior change, and long-term outcomes.
3. **Adherence and Retention:** Investigate strategies to improve participant adherence and retention in diabetes prevention programs. Understand the factors influencing program attrition and develop interventions to enhance engagement, motivation, and long-term commitment.
4. **Comparative Effectiveness:** Conduct comparative effectiveness research to compare different types of diabetes prevention programs, such as group-based interventions, individual counseling, online programs, or community-based initiatives. Evaluate their relative efficacy, cost-effectiveness, and suitability for different populations.

Monitoring and evaluating the impact of the guideline

There are potential indicators that can be used to monitor and evaluate the success of implementing a diabetes prevention program through the Egyptian Health Council (EHC). These indicators can provide complementary information and a more comprehensive assessment of the program's effectiveness.

1. **Changes in Body Mass Index (BMI):** Track changes in average BMI or the proportion of individuals classified as overweight or obese within the target population. Obesity is a significant risk factor for developing type 2 diabetes, and a reduction in BMI indicates improvements in weight management and overall health.

2. **Blood Glucose Control:** Measure average blood glucose levels or the proportion of individuals with well-controlled blood glucose within the target population. Improved blood glucose control indicates better management of diabetes risk factors and reduced progression to diabetes.
3. **Program Engagement and Participation:** Evaluate the level of engagement and participation in the prevention program, including attendance rates for educational sessions, participation in physical activity programs, and utilization of support resources. Higher engagement indicates increased program reach and potential effectiveness.

Updating of the guidelines:

These guidelines will be updated whenever there is new evidence.

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Adapted from ADA “Standards of Care in Diabetes” 2024

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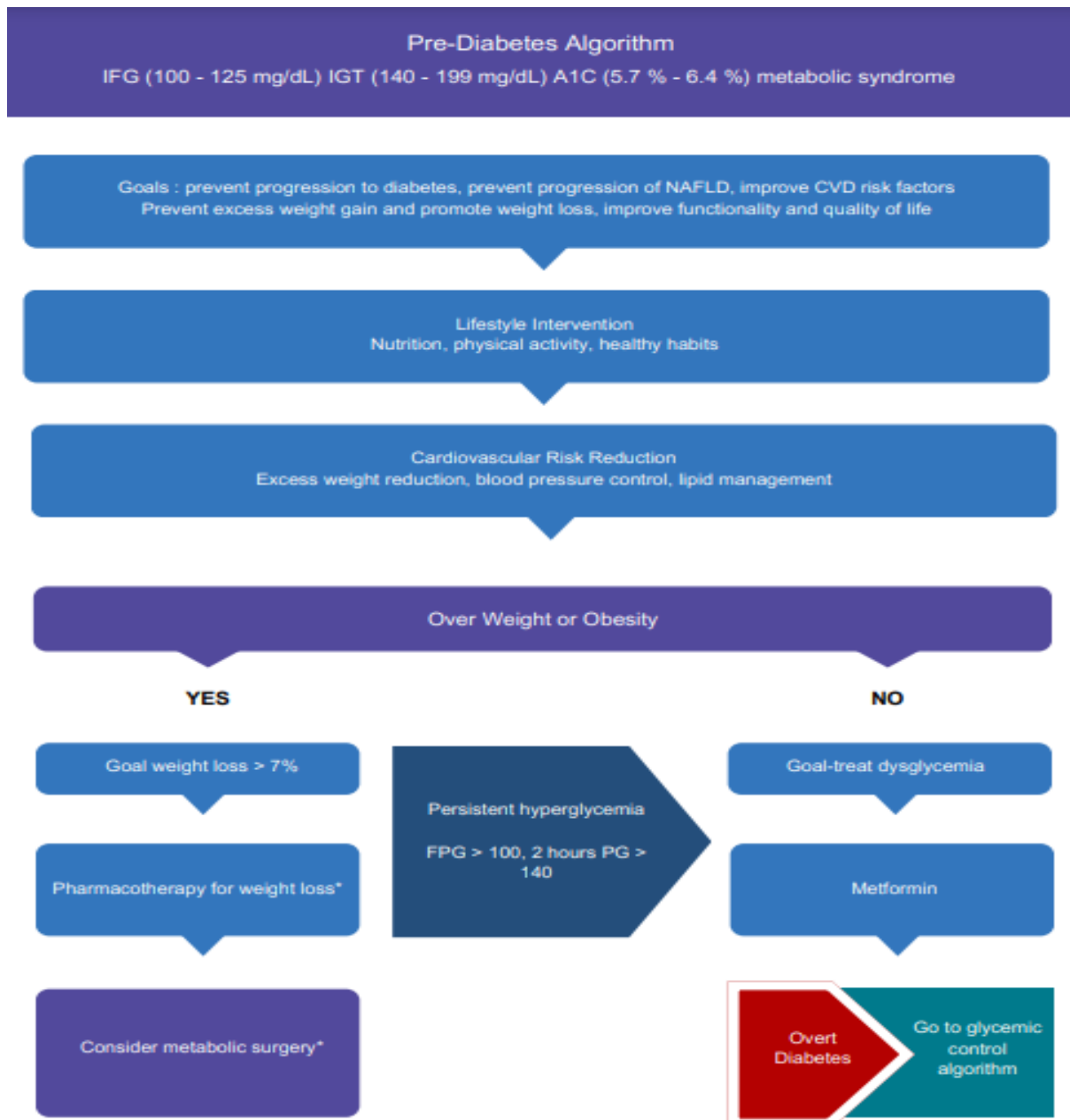
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Appendix 1
Further readings

-Mediterranean diet and diabetes <https://patientinfo.org.au>

--Rational for the use of a Mediterranean diet in diabetes management <https://diabetesjournals.org>

-Nutritional recommendation for individuals with diabetes <https://www.ncbi.nlm.nih.gov>
 -DASH eating plan: An eating pattern for diabetes management diabetesjournals.org



*Pharmacotherapy for weight loss and Metabolic surgery whenever feasible
 *Pharmacological TT to achieve weight loss more than 7%
 Pharmacotherapy discussed in details in obesity chapter

adopted from the American Association of Clinical Endocrinology of Consensus (AACE) - 2023

Pre-diabetic

FPG 100- 125 mg/dl
2-h PG 140- 199 mg/dl
A1C 5.7- 6.4%



Please Note That: These pre-diabetic interventions are not intended for children, adolescents.

Refer For Lifestyle Interventions

Goals 5-7% weight loss and at least 150 minutes of physical activity per week

- Dietitian or lifestyle coach for individualized nutrition, weigh loss and physical activity plan.

Consider Metformin (If lifestyle interventions are unavailable or unsuccessful)

Treat with 500 -2000 mg /day or less if unable to tolerate dosage. Side effects: diarrhea, bloating, B12 deficiency

Metformin is particularly effective in individuals:

- History of gestational diabetes mellitus (GDM)
- BMI $\geq 35\text{kg/mg}^2$
- FPG ≤ 110 mg/dl