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UNITE FOR DIABETES PHILIPPINES

Philippine Practice Guidelines on the
Diagnosis and Management of Diabetes Mellitus

A Project of

UNITE FOR Diabetes Philippines:
A Coalition of Organizations Caring for Individuals with Diabetes Mellitus

Diabetes Philippines (Formerly Philippine Diabetes Association)
Institute for Studies on Diabetes Foundation, Inc (ISDFI)
Philippine Center for Diabetes Education Foundation (PCDEF)
Philippine Society of Endocrinology and Metabolism (PSEM)

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Objectives of the Clinical Practice Guidelines (CPG) on Diabetes Mellitus (DM) Development Initiative

To develop clinical practice guidelines on the screening, diagnosis, and management of diabetes mellitus that reflect the current best evidence and include local data into the recommendations, in view of aiding clinical decision making for the benefit of the Filipino patient

Epidemiology of Diabetes in the Philippines

The prevalence of diabetes mellitus in the Philippines for the last 10 years according to the National Nutrition and Health Survey is as follows:

	1998	2003	2008
FBS >125	3.9	3.4	4.8
DM based on history	---	2.6	4.0
FBS or OGTT or History	---	4.6	7.2%

This figure balloons to 17.8% or nearly 20% after adding those who have pre-diabetes (impaired fasting glucose or impaired glucose tolerance or both) which has a prevalence of 10.6%. One out of every 5 Filipino could potentially have diabetes mellitus or pre-diabetes.

Scope of the Guidelines

The main focus of this set of guidelines is the outpatient management of adult patients with Type 2 diabetes mellitus. Type 1 diabetes will only be briefly mentioned in relation to screening and diagnosis. Its management will not be tackled as Type 1 diabetic patients are typically under the care of physicians with more specialized training such as endocrinologists or diabetologists. Likewise, the management of diabetes in children will not be covered. Finally, guidelines on the inpatient management of diabetes mellitus will not be included in this document but will be developed in future clinical practice guidelines.

The guideline statements will cover four general areas:

1. Screening and Diagnosis of Diabetes
2. Screening for and Prevention of Complications
3. Treatment (Pharmacologic and Non-pharmacologic) of Diabetes
4. Special Populations: Gestational Diabetes, Diabetes in the Elderly

Intended Users

These guidelines are intended for all physicians who are caring for patients with diabetes including diabetologists, endocrinologists, general practitioners, family physicians and general internists, as well as for medical students, resident trainees of internal medicine or family medicine, and endocrinology or diabetology fellows-in-training.

Anatomy of Guidelines

Each of the guideline statements will follow this structure:

- Question or Issue
- Statement of the Guideline Recommendation
- Summary of Evidence
- Evidence Grade
- Strength of Recommendation
- Comparison with other guidelines

Keywords: Clinical practice guidelines, diabetes mellitus, Philippines

Executive Summary

Clinical practice guidelines are easy-to-use statements that bring together the best external evidence (research) and clinical experience for rational decision making about a specific health problem. These evidence-based guidelines should ideally be cost-effective, adapted to the local setting, incorporate patient's values in decision making, and in a developing country like the Philippines, consider issues of equity. In drafting the guidelines, there was a conscious effort to write it not only for those who could afford the tests and treatments, but also for those who may neither have access nor financial means.

This CPG used two main methods for guideline development: (1) Guideline adaptation using the ADAPTE process (ADAPTE, 2007); and (2) de novo development of guideline statements whenever there are no guidelines on certain issues. The latter is the strategy used for developing statements regarding the use of alternative methods for diagnosis of diabetes and herbal medications or alternative medicines for the treatment of diabetes mellitus.

The rationale for the ADAPTE process is to take advantage of existing guidelines and reduce duplication of effort, thereby shortening the amount of time needed for guideline generation.

"The **ADAPTE process** provides a systematic approach to adapting guidelines produced in one setting for use in a different cultural and organizational context. The process has been designed to ensure that the adapted guideline not only addresses specific health questions relevant to the context of use but also is suited to the needs, priorities, legislation, policies, and resources in the targeted setting. The ADAPTE process has been developed to meet the needs of different user groups, including guideline developers, health care providers, and policy makers at the local, national, and international level, as well as groups with lesser or greater resources interested in developing or implementing guidelines. The process is designed to be flexible, depending on the application. The transparent and explicit reporting of the adaptation process if followed will enhance the quality and validity of the adapted guideline." (ADAPTE, 2007) (Appendix A)

Local researches on epidemiology, prognosis, and clinical trials (for drugs and interventions) on diabetes mellitus will be included in the review of evidence whenever available. Sources for local literature are the research database of the Philippines Society of Endocrinology and Metabolism; the list of abstracts of researches of the Institute for Studies on Diabetes Foundation, Inc (ISDFI); the Philippine Council for Health Research and Development (PCHRD) HERDIN database; and the local journal of the Philippine College of Physicians, the Philippine Journal of Internal Medicine.

At the end of this CPG development process, gaps in research and opportunities for improvement in the way we care for diabetic patients will be identified.

The following are the steps in the development of clinical practice guidelines:

Step 1: Research Question Generation

The technical and administrative groups, and other members of the four organizations in UNITE for DM held a meeting to define the scope of the CPG. Questions were developed covering four general areas:

1. screening and diagnosis of diabetes;
2. follow-up care and screening for complications;
3. prevention and treatment of diabetes and
4. gestational diabetes.

This volume will only cover the first section of the practice guideline, which has already been presented and approved by stakeholders.

Research questions will also tackle issues for special populations like pregnant women (gestational diabetes), children (diagnosis and screening of diabetes in children, and prevention of Type 2 DM) and the elderly (targets for control, precautions in the use of anti-diabetic agents).

Step 2: Search and Retrieval of Guidelines

We began the guideline development by searching the National Guideline Clearing House (www.guideline.org), MEDLINE in PUBMED (www.ncbi.nlm.nih.gov) in September 2008. From the National Guideline clearing house using the key term "diabetes"; a total of 515 guidelines were listed. From MEDLINE using the key terms "diabetes", "diabetes mellitus" and "practice guidelines" 129 guidelines on diabetes were identified. These search results were merged and unified to eliminate duplicate publications. References that were not guidelines were eliminated. Subsequently, only 152 guidelines were left.

These guidelines were then assessed using predetermined criteria as follows:

Inclusion Criteria:

a. Guideline must be about diabetes in the outpatient setting
b. General guidelines covering the entire scope of diabetes as well as guidelines covering specific types will also be retrieved: pre-conception care, GDM, prevention of DM, foot care, prevention of complications
c. Published (in text or online) since the details of the review must be available
d. Written in English or with English translation
e. Published in the last five years (2003- onwards) to ensure that evidence base is current. In case that the guideline has an update, then both the original guideline and the update will be retrieved and reviewed.
f. Only evidence-based guidelines will be included (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence)
g. Only national and/or international guidelines will be included (see exclusion b)

Exclusion

a. For duplicate guidelines (e.g., update or revision of previous guidelines) reviewers will only consider the most current
b. Guidelines commissioned by or published by HMO's will not be included since the intent and the use of these guidelines is different from the intended users of this guideline
c. Guidelines for special situations which may be unique to the western population will not be included e.g., care of institutionalized patients, homeless, nursing homes, etc.
d. Guidelines written by a single author not on behalf of an organization; in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input
e. 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 inclusion and exclusion criteria were used to assess each of the guidelines. After applying these criteria only 41 guidelines were left. The 41 guidelines were again reviewed and another 5 were removed from the list because they did not fulfill the inclusion criteria (post-transplant DM guidelines; use of antipsychotics; diabetes in the long-term care setting; DKA guidelines in children; pre-gestational DM –consensus statement only) leaving 36 guidelines.

The breakdown of the 36 guidelines are as follows:

General	10
Foot Care in DM	4
Pre-GDM	6
Hypertension in DM	4
Lipids in DM	4
Diet	4
Prevention of DM	4

The 10 clinical practice guidelines which dealt with comprehensive aspects of diabetes management (labeled as "general" guidelines) included:

1. American Association of Clinical Endocrinologists 2007 (AACE)
2. American Diabetes Association Standards of Medical Care 2010 (ADA)
3. ADA-EASD Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy 2009 - Eventually removed because it is not a practice guideline
4. Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation Western Pacific Region 2005 (IDF West Pac)
5. American College of Physicians 2007 (ACP)
6. Canadian Diabetes Association 2008 (CDA)
7. European Society of Cardiology and European Association for the Study of Diabetes Consensus Statement 2009 (ESC-EASD) - Eventually removed from the list because it is not a guideline
8. International Diabetes Federation Global Guideline 2005 (IDF)
9. Ministry of Health, Singapore 2006 (MOH Sg)
10. Ministry of Health and New Zealand Guidelines Group 2003 (NZGG)

We also included the Type 2 Diabetes guidelines from National Collaborating Centre for Chronic Condition guideline published in 2008 and updated by the National

Institute for Health and Clinical Excellence (NICE) in 2009. This was not populated in the search results of the systematic literature research initially done.

Although many of the general guidelines already include statements on diabetes in children, additional references were retrieved using the key terms, "diabetes mellitus" and "children OR child OR pediatric OR less than 18 years". An additional 17 guidelines were retrieved; however, only 3 of them fulfill the inclusion and exclusion criteria.

Again, for GDM, many of the general guidelines already include recommendations regarding this problem. We were able to identify an additional 7 guidelines on GDM.

As the guideline development process progressed, updates of some of the international guidelines were completed and published. These updates were retrieved and are incorporated into the local CPG whenever applicable.

Step 3: Assess Guidelines Using the AGREE Tool for Critical Appraisal (focusing on Rigour of Methodologic Development)

The Appraisal of Guidelines Research & Evaluation (AGREE) instrument provides a framework for assessing the quality of clinical practice guidelines. The AGREE tool is the method that is recommended by the ADAPTE process for assessing the quality of the clinical practice guidelines that were retrieved. This checklist consists of 23 items that are used to assess the methods used for developing the guideline and the quality of the reporting. (Appendix C)

Each guideline was assessed by at least 2 members of the Technical Review Committee (TRC) using the AGREE tool. Each of the 23 items was evaluated and then an overall assessment was made. The following aspects of the guidelines were assessed using the AGREE tool:

1. Scope and Purpose – 3 items
2. Stakeholder Involvement – 4 items
3. Methodology (Rigour of Guideline Development) – 7 items
4. Clarity and Presentation – 4 items
5. Applicability – 3 items
6. Methodology (Funding and Conflicts of Interest) – 2 items

After appraising the 23 items, an overall recommendation was made. This overall assessment item allows appraisers to make a judgment on the quality of the guideline as a whole, as to whether they would 'strongly recommend,' 'recommend with alterations,' 'would not recommend,' or are 'unsure' about recommending the guideline. A training resource toolkit is available on the AGREE web site, www.agreetrust.org.

Step 4: Decide and Select Guidelines for Inclusion

At the onset of the project, the TRC members decided on the following criteria for inclusion of studies based on the outcome of the appraisal process using AGREE:

1. Should obtain a grade of 3 in at least 4 of the 7 categories of rigour
2. Should also obtain an overall rating of at least 60%
3. Obtain an overall assessment of strongly recommend or recommend with alterations.

A guideline will be included if all 3 criteria are fulfilled. Two out of the 11 clinical practice guidelines were excluded:

1. The Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation Western Pacific Group guideline which obtained a score of 34. 52% for methodologic rigour and had a consistent overall recommendation of "would not recommend" for the 4 reviewers
2. The Ministry of Health, Singapore clinical practice guideline which obtained a score of 52.38% for rigour of methodology and with 4 categories having a score average of 2. Regarding the overall assessment, 2 out of 4 reviewers gave a "recommend with alterations" rating while 2/4 gave a rating of "unsure".

The final list of guidelines included the following:

1. American Association of Clinical Endocrinologists 2007 (AACE)
2. American Diabetes Association Standards of Medical Care 2010 (ADA)
3. American College of Physicians 2007 (ACP)
4. Canadian Diabetes Association 2008 (CDA)
5. International Diabetes Federation Global Guideline 2005 (IDF)
6. Ministry of Health and New Zealand Guidelines Group 2003 (NZGG)
7. National Collaborating Centre for Chronic Conditions 2008 (NCCCC)

Step 5: Draft Guideline Report

The research questions were then answered by obtaining the guideline statements from the 8 CPGs which were tabulated and summarized, noting both the actual content (the statement giving the recommendation), and the levels of evidence and strengths of the recommendation. Subsequently, a draft statement for each question was made with a corresponding strength of recommendation based on the levels of evidence. The original evidence or references used as the basis for the statements were also retrieved by the TRC to ensure that the grade of the evidence given in the original guidelines were correct.

The UNITE for DM CPG used the Oxford Centre for Evidence-Based Medicine Levels of Evidence (March 2009) for grading the levels of the evidence and the strength of recommendations (Appendix D: CEBM Levels of Evidence and Strength of Recommendation). Briefly, the levels of the evidence are graded according to Arabic numerals 1-5, considering the hierarchy of literature (e.g., for questions of therapeutic efficacy, randomized controlled trials are ranked higher than non-blinded or non-randomized trials or observational studies).

The strength of the guideline recommendation is indicated by the letters A to D as follows:

- Grade A is the strongest recommendation based on consistent level 1 studies (**strong recommendation** to use or not to use an intervention or test);
- Grade B strength is derived from consistent level 2 or 3 studies or extrapolations from level 1 studies (**moderately strong recommendation**);
- Grade C strength is from level 4 studies or extrapolations from level 2 or 3 studies (**intermediate strength of recommendation**); and
- Grade D is based on level 5 evidence or troublingly inconsistent or inconclusive studies of any level (**weak recommendation**).

Philippine PRACTICE GUIDELINES FOR DIABETES MELLITUS Part 1:

SCREENING AND DIAGNOSIS

CLASSIFICATION OF DIABETES

Issue 1a. How is diabetes classified?

Diabetes mellitus is classified into four major clinical types according to etiology:

- Type 1 diabetes mellitus (formerly insulin dependent diabetes mellitus or Juvenile diabetes mellitus): results from auto-immune beta-cell destruction, leading to absolute insulin deficiency. Typically but not exclusively in children.
- Type 2 diabetes mellitus (formerly non-insulin dependent diabetes mellitus or adult-onset DM): results from a progressive insulin secretory defect on the background of insulin resistance
- Gestational diabetes mellitus (GDM): diabetes first diagnosed during pregnancy
- Secondary diabetes e.g., genetic defects in beta cell function or insulin action, diabetes of the exocrine pancreas (pancreatitis, cystic fibrosis), drug- or chemical-induced diabetes (such as from the treatment of AIDS, after organ transplantation, glucocorticoids), other endocrine diseases (Cushing's syndrome, hyperthyroidism)

References:
1. Diabetes Care, Volume 31, Supplement 1, January 2008.
2. Diabetes Care, Volume 32, Supplement 1, January 2009.
3. Standards of Medical Care in Diabetes- 2010. Diabetes Care, Volume 33, Suppl 1, January 2010

Issue 1b. How can one differentiate between the 2 major types of diabetes, Type 1 and Type 2 diabetes mellitus?

Differentiation between the 2 major types of diabetes mellitus may be difficult in younger individuals but is important since the diagnosis is the basis for therapy. Type 1 diabetics are insulin dependent and need to be maintained on combinations of prandial and basal insulin for life. Ideally, they also need to be under the care of diabetes specialists. Type 2 diabetes is usually managed by using oral agents, but some Type 2 diabetics will also require insulin to attain good control. The table below, from the International Diabetes Federation Western Pacific Region Guidelines 2005 outlines the differentiation between the 2 major forms of diabetes, although some tests like the antibodies and C-peptide are not available in some areas of the Philippines.

Table 1. Differentiation between Type 1 and Type 2 Diabetes Mellitus, especially in younger individuals

Characteristics	Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Onset	Acute-symptomatic	Slow-often-asymptomatic
Clinical Picture	Weight loss, polyuria, polydipsia	If symptomatic, similar picture as T1 DM- weight loss, polyuria, polydipsia • Obese • Strong family history of T2DM • Polycystic ovary syndrome (PCOS)
Ketosis	Almost always present	Usually absent
C-Peptide	Low/absent	Normal/elevated
Antibodies	• ICA positive • Anti-GAD positive • ICA 512 positive	• ICA negative • Anti-GAD negative • ICA 512 negative
Therapy	Insulin	Lifestyle, oral anti-diabetic agents, insulin
Associated auto-immune diseases	Yes	No

Adapted from Alberti Diab Care, 2004.8
ICA – islet cell antibodies; Anti-GAD – glutamic acid decarboxylase antibodies

SCREENING AND TESTING FOR DIABETES IN ASYMPTOMATIC INDIVIDUALS

Issue 2: Should universal screening be done and how should screening be done?

- All individuals being seen at any physician's clinic or by any healthcare provider should be evaluated annually for risk factors for type 2 diabetes and pre-diabetes. (Table 1) (Level 5, Grade D)
- Universal screening using laboratory tests is not recommended as it would identify very few individuals who are at risk. (Level 5, Grade D)

Issue 3.1: Who should undergo laboratory testing for diabetes/prediabetes?

Laboratory testing for diabetes and prediabetes is recommended for individuals with any of the risk factors for Type 2 diabetes mellitus. (Table 1) (Level 3-4, Grade B)

Table 2. Demographic and Clinical Risk Factors for Type 2 DM

- Testing should be considered in all adults ≥40 yo
- Consider earlier testing if with at least one other risk factor as follows:
  - o History of IGT or IFG
  - o History of GDM or delivery of a baby weighing 8 lbs or above
  - o Polycystic ovary syndrome (PCOS)
  - o Overweight: Body Mass Index (BMI)[2] of ≥23 kg/m^2 or Obese: BMI of ≥25 kg/m^2, or
  - o Waist circumference ≥80 cm (females) and ≥90 cm (males), or Waist-hip ratio (WHR) of ≥1 for males and ≥0.85 for females
  - o First degree relative with Type 2 diabetes
  - o Sedentary lifestyle
  - o Hypertension (BP ≥140/90 mm Hg)
  - o Diagnosis or history of any vascular diseases including stroke, peripheral arterial occlusive disease, coronary artery disease
  - o Acanthosis nigricans
  - o Schizophrenia
  - o Serum HDL <35 mg/dL (0.9 mmol/L) and/or
  - o Serum Triglycerides >250 mg/dL (2.82 mmol/L)

Summary of Evidence:

All CPGs reviewed recommend laboratory testing for confirmation in individuals at risk for diabetes mellitus. ADA, CDA and AACE specifically enumerated the risk factors for diabetes, with concordance among the 3 CPGs regarding the majority of risk factors.

According to CDA 2008 recommendation, although the relatively low prevalence of diabetes in the general population makes it unlikely that mass screening will be cost-effective, testing for diabetes in people with risk factors for type 2 diabetes or with diabetes-associated conditions is likely to result in more benefit than harm and will lead to overall cost savings. Routine testing for type 2 diabetes is, therefore, justifiable in some, but not all settings.

The ADA 2010 recommends routine testing for all individuals age 45 years old and above. CDA 2008 recommends routine laboratory testing for all adults age 40 and above which has proved to be useful in detecting unrecognized diabetes. In the Philippines, the 7th National Nutrition and Health Survey of 2008 showed that the significant burden of diabetes begins at age 40 years, approximating the national prevalence. In a 2002 study by Baltazar, et al, among Luzon residents, the over-all prevalence of diabetes was 5.1% with a sharp rise in trend noted at 40 years and above.

Among the risk factors enumerated, **presence of IGT, IFG, PCOS, and history of GDM are correlated strongly with DM occurrence** (Table 3).

Table 3. Risk Factors for Diabetes Mellitus and Their Corresponding Strengths of Association.

Risk Factors	Strength of Association
Previously identified IGT or IFG	both IFG and IGT RR* 12.13 (4.27-20.00) isolated IGT RR 5.52 (3.13-7.91) isolated IFG RR 7.54 (4.63-10.45)
GDM	RR 7.43 (4.79-11.51)
PCOS	OR for IGT (BMI-matched) 2.54 (1.44-1.47) OR for DM2 (BMI-matched) 4.00 (1.97- 8.10)
Overweight or obesity	BMI >25 kg/m^2 (OR men 1.52, women 1.59) WC >90 cm for males and >80 cm for females (OR men 1.54,women 1.70) Waist-hip ratio >1 for males and >0.85 for females (OR men 1.53, women 1.50)
First-degree relative with DM (parents or siblings)	OR 2.13 (1.22-3.71)
Sedentary lifestyle	RR for DM based on average hours spent watching TV per week (0-1, 2-10, 11-20, 21-40, >40): RR 1.00, 1.66, 1.64, 2.16, and 2.87
Conditions assoc with insulin resistance (acanthosis nigricans)	OR 1.97 (1.18-3.27)
HPN	Increased blood pressure, per 1 SD: Systolic: RR 1.56 (1.31-1.85) Diastolic: RR 1.52 (1.27-1.83)
CVD	DM as a CVD risk factor (age- and sex-adjusted): HR 2.5 (1.9 to 3.2)
Schizophrenia	OR 2.07 (1.03 to 4.15)
High TG, low HDL or both	Increased triglycerides, per 1 SD: OR 1.70 (1.62-1.78) Increased apolipoprotein A-I, per 1 SD: OR 0.76 (0.62–0.92)

• RR= relative risk, OR= odds risk

Issue 3.2. In what setting/s should testing for diabetes be done?

- Testing should ideally be carried out within the healthcare setting (clinics, hospitals, local health centers) because of the need for follow-up and discussion of abnormal results by qualified health care professionals (nurse, diabetes educator, physician). (Level 3 , Grade B)
- Testing at any setting should be supervised by a qualified health care professional. (Level 5, Grade D)

Summary of Evidence

ADA 2010 states that "… community screening outside a health care setting is not recommended because of 3 reasons: People with positive tests may not seek, or have access to, appropriate follow-up testing and care; there may be failure to ensure appropriate repeat testing for individuals who test negative; and community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed". The CDA and AACE did not specifically

mention as to what setting it should be done. IDF stated that "Each health service should decide whether to have a programme to detect people with undiagnosed diabetes ... based on prevalence of undiagnosed diabetes and on resources available to conduct the detection programme and treat those who are detected."
No randomized controlled trials (RCT's) regarding screening have been conducted. Population-based and selective screening programs in community settings (outreach programs, health fairs, or shopping malls) have uniformly demonstrated low yield of <1% and poor follow-up.

Issue 3.3 If initial test/s are negative for diabetes, when should repeat testing be done?

- Repeat testing should ideally be done annually. (Level 5, Grade D)

Summary of Evidence

The ADA 2010, CDA 2008 and IDF 2005 are of the opinion to do repeat testing at least at 3-year intervals since there is little likelihood that an individual will develop significant complications of diabetes within 3 years of a negative result. The ADA 2010 recommends repeat testing annually for those with IFG and/or IGT. The CDA 2008 recommends more frequent testing in those with multiple risk factors. AACE 2007 recommends annual testing for all those with risk factors.

We recommend repeat testing annually for Filipinos with risk factors owing to the significant prevalence and burden of diabetes in our country. In a local study among newly-diagnosed diabetics in Manila, about 20% already had peripheral neuropathy, 42% had proteinuria, and 2% had diabetic retinopathy.

Summary of Recommendations: Screening for Diabetes Among Asymptomatic Adults

- All individuals being seen at any physician's clinic or by any healthcare provider should be evaluated annually for risk factors for type 2 diabetes and pre-diabetes. (Table 1) (Level 5, Grade D)
- Obesity, pre-diabetes, components of the metabolic syndrome, PCOS, previous GDM, family history and schizophrenia are some of the risk factors for DM.

- **Universal screening using laboratory tests is not recommended as it would identify very few individuals who are at risk.** (Level 5, Grade D)
- Laboratory testing for diabetes and pre-diabetes is recommended for individuals with any of the risk factors for Type 2 diabetes mellitus. (Level 3-4, Grade B)
- Laboratory Testing should be considered in all adults ≥40 years old
- Consider earlier testing if with at least one other (other than age) risk factor for diabetes.

- Testing should ideally be carried out within the healthcare setting (clinics, hospitals, local health centers) because of the need for follow-up and discussion of abnormal results by qualified health care professionals (nurse, diabetes educator, physician). (Level 3, Grade B)
- Testing at any setting should be supervised by a qualified health care professional. (Level 5, Grade D)

- **If initial test/s are negative for diabetes,** then repeat testing should ideally be done annually. (Level 5, Grade D)

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SCREENING AND DIAGNOSIS OF DIABETES IN CHILDREN

Issue 4.1 Should screening be done for Type 1 diabetes mellitus?

Screening for Type 1 DM is not recommended at the moment for the following reasons:

- The disease is of low prevalence although an increasing trend is observed. Exact prevalence/incidence has yet to be established.
- Screening using serologic markers are not readily available and expensive, thus, making screening not cost-effective.
- Since clinical trials for interventions to prevent or delay Type 1 diabetes have not been proven effective,

screening for T1 diabetes is NOT recommended.

Summary of Evidence:

In the Philippines there are no nationwide prevalence or incidence studies on Type 1 diabetes mellitus. A survey done by Castillo-Cruz in a municipality in Bulacan showed only 7 cases of Type 1 DM among children aged 0-14 year old during a 10 year period from 1989 to 1998. In the U.S., the rate of new cases among youth was 19 per 100,000 each year for type 1 diabetes and 5.3 per 100,000 for type 2 diabetes in 2002 to 2003.

Issue 4.2 Should screening for Type 2 DM be done in children?

According to ADA, screening for pre-diabetes and Type 2 DM is recommended among asymptomatic children commencing at age 10 years or at onset of puberty, if puberty occurs at a younger age (ADA) with the following risk factors: (Grade C, Level 4)

- Overweight (BMI >85th percentile for age and sex, weight-for-height >85th percentile, or weight >120% of ideal for height) OR
- Obese: BMI >95th centile or > +2SD
- Plus any 2 of the following risk factors
  - o Family history (especially parents and grandparents) of Type 2 DM
  - o Signs of insulin resistance (Acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small for gestational age birth weight)
  - o Maternal history of diabetes or GDM during the child's gestation

Summary of Recommendations: Screening for Diabetes in children

- Screening for Type 1 diabetes among children is NOT recommended because the disease appears to be of low prevalence; screening tests using serologic markers are not readily available and do not appear to be cost-effective; and there are as yet no clearly effective preventive approaches.
- Screening for pre-diabetes and Type 2 DM is recommended among asymptomatic children commencing at age 10 years or at onset of puberty, if puberty occurs at a younger age (ADA) with risk factors of overweight or obesity, plus any 2 of the following: family history, signs of insulin resistance and maternal history of diabetes or GDM during the child's gestation. (Grade C, Level 4)

DIAGNOSIS OF DIABETES

ISSUE 5.1 What tests and criteria should be used to diagnose diabetes?

The diagnosis of Diabetes Mellitus can be made based on the following criteria*: (Grade B, Level 2)

- Plasma glucose ≥126 mg/dL (7.0 mmol/L) after an overnight fast
  - o Fasting is defined as no caloric intake for at least 8 hours up to a maximum of 14 hours,

or

- Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an Oral Glucose Tolerance Test
- The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water after an overnight fast of between 8 and 14 hours,

or

- A random plasma glucose ≥200 mg/dl (11.1 mmol/l) in a patient with classic symptoms of hyperglycemia (weight loss, polyuria, polyphagia, polydipsia) or with signs and symptoms of hyperglycaemic crisis.

*Among ASYMPTOMATIC individuals with positive results, any of the three tests should be REPEATED within two weeks for confirmation. (Grade C, Level 4)

Summary of Evidence:

All the seven clinical practice guidelines that were evaluated for adaptation and subsequently reviewed for recommendations on screening and diagnosis of DM type 2 advocate the fasting plasma glucose, 75-gram oral glucose tolerance tests and the random blood glucose as potential screening as well as diagnostic tests. The fasting plasma glucose remains a useful tool used for the general population due to its wide availability, lower cost and reproducibility.[1,2] It has a sensitivity ranging from 45 to 60% and a specificity of >90%.[3] The positive predictive value is 26 to 30 when applied in a population with a prevalence of 6% which is close to the NNHES 2008 data on Diabetes Mellitus type 2 prevalence of 7.1% in the Philippines.[4]

Subjects with borderline fasting glucose need a confirmatory 75-gram oral glucose tolerance test since the OGTT 2-hour post load value would lead to greater detection of patients with diabetes at a sensitivity of 90 to 93% and specificity of 100% with a positive predictive value of 47 to 48 across populations with low and relatively higher prevalence of diabetes.[3] Fasting plasma glucose might not detect some patients who are positive with the OGTT.[3, 5, 6, 7, 8]

Issue 5.2 Who should undergo the OGTT as the preferred initial test for screening for diabetes?

A 75-gram OGTT is preferred as the first test in the following individuals who have: (Grade B, Level 3)

- A previous FBS showing Impaired Fasting Glucose (100 to 125 mg/dL or 5.6 to 6.9 mmol/L)
- Previous diagnosis of Cardiovascular Disease (Coronary Artery Disease, Stroke, Peripheral Arteriovascular Disease) or who are at high risk for cardiovascular disease.
- A diagnosis of Metabolic Syndrome

Summary of Evidence:

The American guidelines consider OGTT as an equal alternative to FPG in asymptomatic individuals, or as a second step in those with FPG 100 to 125 mg/dL (5.6 to 6.9 mmol/L). The Canadian and New Zealand guidelines only recommend OGTT as a second step for patients with IFG plus ethnic or other metabolic risk factors citing literature on the link of IFG with other criteria of the metabolic syndrome.[9-13] It is only the IDF

European guideline that gives a specific indication as to the particular group of asymptomatic individuals who will benefit from OGTT as the initial test. The importance of detecting patients with elevated 2-hour post loading glucose level is based on the DECODE study which showed the strong correlation of the 2-hour post loading hyperglycemia in subjects with diabetes with all cause mortality, cardiovascular disease, coronary heart disease, and stroke mortality.[14]

A similar study among the Japanese and Asian Indian population, the DECODA, also showed the greater predictive value of 2-hour post load plasma glucose for premature death, cardiovascular and all-cause mortality.[15]

In the absence of established or previously documented cardiovascular disease, the presence of the metabolic syndrome indicate high risk for CVD that would warrant OGTT as initial test based on two large risk assessment studies among European cohorts that also proved that it is a cost-effective strategy in DM prevention.[16, 17] The relationship of glucose intolerance and cardiovascular risk profiles among 12 Asians countries, including Filipino subjects has also been described in the DECODA study analysis leading to the conclusion that if OGTT is done only in those with IFG, then every fourth patient with DM will be missed, and every second patient with IGT will also be missed, emphasizing that a lower threshold for doing OGTT is needed for the Asian population.[18]

Issue 5.3 Can other laboratory tests be used for the diagnosis of diabetes?

At the present time, we cannot recommend the routine use of the following tests for the diagnosis of diabetes: (Grade C, Level 3)
- HBA1c
- Capillary Blood Glucose
- Fructosamine

However, if a result is available upon consultation due to prior testing, it should be interpreted with caution and should be confirmed by any of the 3 tests that are considered standard: fasting plasma glucose, oral glucose tolerance test or random plasma glucose. (Grade B, Level 2)

We do not recommend the following tests for the diagnosis of diabetes: (Grade B, Level 3)
- Urine glucose
- Plasma Insulin

Summary of Evidence:

HBA1c using a method approved by the National Glycohemoglobin Standardization Program (NGSP) traceable to the reference range (4.0 to 6.0%) used in the Diabetes Control and Complications Trial (DCCT) is recommended for diagnosis and risk assessment only by the American Diabetes Association as of 2010.[19-22] The ADA cut-off for diagnosis is >6.5%, and for patients at risk for DM (pre-diabetes) it is 5.7% to 6.4%. If it cannot be confirmed whether the HBA1c assay used is NGSP certified, as is the situation in almost all parts of the Philippines, then the result cannot be used for diagnosis.

According to the IDF- Europe 2010 evidence-based guideline, a high HBA1c may only identify a fraction of asymptomatic people with DM. It is insensitive in the low range, and a normal HBA1c level cannot exclude the presence of DM or prediabetes.[23] HBA1c was less sensitive for detecting prediabetes or DM compared to OGTT results.[24, 25]

Capillary blood glucose, fructosamine and urine glucose test have lower reproducibility and do not have better yield than the three standard tests (FPG, OGTT, RPG) based on sensitivity, specificity and positive predictive value.[3]

DIAGNOSIS OF PRE-DIABETES

ISSUE 5.4: What criteria can be used to diagnose pre-diabetes?

The criteria for pre-diabetes is:

- Impaired Fasting Glucose defined as FBS of 5.6 mmol/L (100 mg/dL) up to 125 mg/dL or 6.9 mmol/L (Grade B, Level 2)
- Impaired Glucose Tolerance defined as Random/casual blood glucose of 7.7 up to 11.0 mmol/L (140-199 mg/dL) OR 2-hr blood sugar in the 75-gm OGTT equal to 7.7 (140 mg/dL) up to 11.0 mmol/L (199 mg/dL) (Grade B, Level 2)

ISSUE 5.5 What is the criteria for normal blood sugar?

Normal blood is sugar is defined as:

- An FBS <5.6 mmol/L (100 mg/dL), or
- Random/casual blood glucose <7.7 (140 mg/dL), or
- 2-hr blood sugar in the 75-gm OGTT <7.7 (140 mg/dL) (Grade B, Level 2)

Summary of Evidence:

The ADA developed the diagnostic criteria for diabetes based on the occurrence of retinopathy as a microvascular event among subjects not previously diagnosed with diabetes. All the other guidelines are similar to the ADA recommendation.[19, 26, 27] Several Asian studies have also tested these criteria using venous blood samples among their population but using the 2nd-hour OGTT level as standard instead of microvascular outcomes.[28 - 35]

The ADA lowered the threshold for diagnosis of impaired fasting plasma glucose in 2003 in order to approximate the prevalence of IFG similar to IGT.[36] Other groups such as the World Health Organization and the International Diabetes Federation have not adapted this because their reviews of evidence using cardiovascular outcomes mainly among American Caucasian and Europeans showed significant correlation only with IFG level above 6.1 mmol/L or 110 mg/dL.[37 – 42] The NZGG use a different cut-off for IFG that will indicate the need for an OGTT based on ethnicity and race- using the higher cut-off 6.1 mmol/L (110 mg/dL) for European descendants, and 5.6 mmol/L (100 mg/dL) for others. If the endpoint is earlier detection and intervention of pre-diabetes before it progresses to DM, several studies among the Japanese and Thai population noted lower threshold with better ROC at the 5.6 to 6.9 mmol/L (100-125 mg/dL).[34, 43, 44] If the endpoint is the detection of IGT for earlier

cardiovascular risk assessment, then we cite the result of the DECODA group in 12 Asian countries including the Philippines that recommends a lower threshold for doing OGTT among Asians as previously discussed.[15, 18]

If initial test/s are negative for diabetes, repeat testing should ideally be done annually. (Grade D, Level 5)

In some countries, 20% to 50% of cases already have complications at the time of diagnosis.[45] The international guidelines recommend repeat testing from one to three years depending on co-existence of other risk factors. In the Philippines, one study cohort showed that 42% of newly diagnosed DM type 2 patients already have proteinuria, 20% already have peripheral neuropathy, and 12% already have clinically significant retinopathy.[46] We recommend that patients at risk should therefore be tested more frequently, at least annually if initial tests are negative.

Summary of Recommendations: Diagnosis of Diabetes and Pre-diabetes

- The diagnosis of Diabetes Mellitus can be made based on the following criteria*: (Grade B, Level 2)
  - Fasting Plasma glucose ≥126 mg/dL (7.0 mmol/L) after an overnight fast for at least 8 hours up to a maximum of 14 hours, or
  - Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during a 75-gm Oral Glucose Tolerance Test, or
  - A random plasma glucose ≥200 mg/dl (11.1 mmol/l) in a patient with classic symptoms of hyperglycemia (weight loss, polyuria, polyphagia, polydipsia) or with signs and symptoms of hyperglycaemic crisis.

Among ASYMPTOMATIC individuals with positive results, any of the three tests should be REPEATED within two weeks for confirmation. (Grade C, Level 4)

- A 75-gram OGTT is preferred as the first test in the following individuals who have: (Grade B, Level 3)
  - A previous FBS showing Impaired Fasting Glucose (100 to 125 mg/dL or 5.6 to 6.9 mmol/L)
  - Previous diagnosis of Cardiovascular Disease (Coronary Artery Disease, Stroke, Peripheral Arteriovascular Disease) or who are at high risk for cardiovascular disease.
  - A diagnosis of Metabolic Syndrome

- At the present time, we cannot recommend the routine use of the following tests for the diagnosis of diabetes: (Grade C, Level 3)
  - HBA1c (because of poor access and lack of standardiazation)
  - Capillary Blood Glucose
  - Fructosamine

However, if a result is available upon consultation due to prior testing, it should be interpreted with caution and should be confirmed by any of the 3 tests that are considered standard: fasting plasma glucose, oral glucose tolerance test or random plasma glucose. (Grade B, Level 2)

- We do not recommend the following tests for the diagnosis of diabetes (Grade B, Level 3): Urine glucose and Plasma Insulin

- The criteria for pre-diabetes is:
  - Impaired Fasting Glucose defined as FBS of 5.6 mmol/L (100 mg/dL) up to 125 mg/dL or 6.9 mmol/L (Grade B, Level 2)
  - Impaired Glucose Tolerance: casual blood glucose of 7.7 up to 11.0 mmol/L (140-199 mg/dL) OR 2-hr blood sugar in the 75-gm OGTT equal to 7.7 (140 mg/dL) up to 11.0 mmol/L (199 mg/dL) (Grade B, Level 2)

- Normal blood is sugar is defined as:
  - An FBS <5.6 mmol/L (100 mg/dL), or
  - Random/casual blood glucose <7.7 (140 mg/dL), or
  - 2-hr blood sugar in the 75-gm OGTT <7.7 (140 mg/dL) (Grade B, Level 2)

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SCREENING AND DIAGNOSIS OF DIABETES IN PREGNANT WOMEN

Issue 6.1 Should universal screening for diabetes be done among pregnant women?

All pregnant women should be screened for gestational diabetes (Grade B, Level 2).

Summary of Evidence:

ADA recommends screening for all except very low risk women, i.e., those belonging to an ethnic group with a low prevalence of diabetes. Filipino women will not fall under the low risk category as data from the ASGODIP (AFES Study Group on Diabetes in Pregnancy) has shown a prevalence of 14% in 1203 pregnancies[2]. Furthermore in a UK cohort, relative risk was increased sevenfold for women of South East Asian descent (RR 7.6 [95%CI 4.1,14.1])[3]. **Hence, universal screening should apply in our population.** The DIPSI guideline also recommends universal screening for Indian women, because of the high prevalence of gestational diabetes in their population[4].

The National GDM Technical Working Party of New Zealand recommends that all pregnant women be offered screening for GDM[5]. The NICE guideline recommendation is similar to that of the ADA where testing is offered to women with any risk factor for gestational diabetes[6].

Screening is undertaken to detect disease and to provide early care that morbidity and mortality may be avoided.

Gestational diabetes has been associated with increased risk of perinatal morbidity: macrosomia, shoulder dystocia, birth injuries and hypoglycemia. Subsequently these infants have a higher risk of abnormal glucose tolerance and obesity.

Screening for gestational diabetes and treatment to reduce maternal glucose levels has been shown to be beneficial in the Australasian Carbohydrate Intolerance Study (ACHOIS)[7]. In the intervention group, the rate of serious perinatal complications was significantly decreased as compared to routine care (RR 0.33 [95% CI 0.14-0.75], p=0.01). Treatment of even mild gestational diabetes[8], defined as fasting glucose below 95 mg/dL on screening OGTT, has also been shown to reduce the risks of fetal overgrowth (RR 0.41 [97% CI 0.26,0.66], p<0.001) and shoulder dystocia (RR 0.37 [97% CI 0.14.0.97], p=0.02).

Gestational diabetes has also been associated with preeclampsia/gestational hypertension and an increased rate of cesarean sections. Women with a history of gestational diabetes are also at an increased risk to develop type 2 diabetes. The trial on mild gestational diabetes also showed decreased risk for cesarean delivery (RR 0.79 [97%CI 0.64, 0.99], p=0.02) and hypertensive disorders (RR 0.63 [97%CI 0.42,0.96], p=0.01) for the women in the intervention group[8].

Screening for GDM identifies a group of young women at risk of developing type 2 diabetes allowing early and targeted intervention. A study looking at risk factors for development of type 2 diabetes in a Filipino-American population found gestational diabetes to be an independent risk factor (OR 21.65 [95% CI 6.73,69.67])[9]. In a cohort of Filipino women followed up 2 years after a GDM pregnancy, nearly half had abnormal glucose tolerance (16.9% with type 2 diabetes and 32% with impaired glucose tolerance)[10]. A meta-analysis involving 675,455 women and 10,859 type 2 diabetic events showed that women with gestational diabetes had an increased risk of developing type 2 diabetes (RR 7.43, 95% CI 4.79-11.51)[11]. Once identified, women with GDM benefit from intensive lifestyle and metformin therapy which reduce the incidence of diabetes by approximately 50%[12].

Issue 6.2 When should screening be done for pregnant women?

All pregnant women should be evaluated at the first prenatal visit for risk factors for diabetes (Grade C, Level 4).

Summary of Evidence:

The ADA recommends that a woman's risk for gestational diabetes be assessed at the first prenatal visit, as those at high risk are offered testing at this visit[1]. The NZGG also recommends risk stratification where "women at high risk of undiagnosed type 2 diabetes should be screened at booking.[5]" The NICE guideline recommends that "women who have had gestational diabetes in a previous pregnancy should be offered early self-monitoring of blood glucose or an OGTT at 16-18 weeks.[6]"

Table 4 shows risk factors for diabetes among pregnant women. The odds ratios and positive predictive values from the literature are provided. Note that the ADA[1] defines macrosomia as birth weight more than 4000 grams while the ASGODIP sets a cutoff equivalent to 3600 grams.[13] .

Table 4. Risk Factors for Diabetes Among Pregnant Women

Prior history of GDM	OR 23.6 [95%CI 11.6, 48.0][13]
Glucosuria	OR 9.04 [95%CI 2.6, 63.7][15]; PPV 50%[16]
Family history of diabetes	OR 7.1 [95%CI 5.6, 8.9]; OR 2.74 [95%CI 1.47, 5.11][14]
First-degree relative with type 2 diabetes	PPV 6.7%[16]
First-degree relative with type 1 diabetes	PPV 15%[16]
Prior macrosomic baby	OR 5.59 [95%CI 2.68, 11.7][14]
Age >25 years old	OR 1.9 [95%CI 1.3, 2.7][17]; OR 3.37 [95%CI 1.45, 7.85][14]
Diagnosis of polycystic ovary syndrome	OR 2.89 [95%CI 1.68, 4.98][18]
Overweight/obese before pregnancy	
BMI >27 kg/m^2	OR 2.3 [95%CI 1.6, 3.3][17]
BMI >30 kg/m^2	OR 2.65 [95%CI 1.36, 5.14][14]
Macrosomia in current pregnancy	PPV 40%[16]
Polyhydramnios in current pregancy	PPV 40%[16]
Intake of drugs affecting carbohydrate metabolism	

Legend: OR: Odds Ratio PPV: Positive Predictive Value

High-risk women should be screened at the soonest possible time (Grade B, Level 3).

Summary of Evidence:

A woman with any of the above risk factors is considered high risk. The ADA defined the criteria for very high risk as follows: severe obesity, prior history of GDM or delivery of LGA infant, presence of glucosuria, diagnosis of PCOS and strong family history of type 2 diabetes[1]. The NICE guideline considers women with previous history of GDM as high risk[6].

Early screening is feasible as according to the DIPSI guideline as "the fetal beta cell recognizes and responds to maternal glycemic level as early as 16th week of gestation.[4]" However, the US Preventive Services Task Force (USPSTF) identified no randomized controlled trials on screening and treatment of gestational diabetes before 24 weeks of gestation[19]. Nonetheless, one prospective cohort study showed that women with

early-onset GDM were likely to be hypertensive (18.5% vs 5.9%, p=0.006) and to have need of insulin therapy (33.8% vs 7.1%, p=.0000) as compared to women who developed GDM later[20].

Routine testing for gestational diabetes is recommended at 24 to 28 weeks age of gestation for women with no risk factors (Grade B, Level 3).

Summary of Evidence

Women without risk factors should still be screened. In an observational study, more than one-third of women with gestational diabetes who had no historical risk factors would have been missed if only those with risk factors were tested.

The US Preventive Services Task Force (USPSTF) found no evidence that screening after the 24th week leads to reduction in morbidity and mortality[19]. However, the ACHOIS provides evidence that treatment of GDM after the 24th week of gestation does reduce complications[7]. The ADA recommends screening "greater than low-risk women" for gestational diabetes at 24 to 28 weeks gestation[1]. The NICE guideline states that women with any risk factor other than previous gestational diabetes, should be offered an OGTT at 24-28 weeks[6].

Testing for gestational diabetes should still be carried out in women at risk, even beyond 24 to 28 weeks age of gestation (Grade C, Level 3).

Summary of Evidence:

ASGODIP data has shown that as much as 3.6% of low-risk and 40.4% of high-risk women are diagnosed to have gestational diabetes when testing is done beyond the 26th week[21]. In the ASGODIP cohort from the Cardinal Santos Medical Center, more than 75% of their GDM cases were diagnosed from the 26th to 38th weeks of gestation, with more of these women delivering macrosomic infants[22]. In the ASGODIP cohort from Veterans Memorial Medical Center, half of the GDM cases were diagnosed between the 31st to 40th weeks of gestation[23].

Issue 6.3 Which tests should be used to screen pregnant women for gestational diabetes?

An oral glucose tolerance test (OGTT), preferably the 75-g OGTT, should be used to screen for gestational diabetes (Grade B, Level 3). [see appendix for methodology of the 75-gm OGTT for pregnant women]

Summary of Evidence:

Both the NICE[6] and DIPSI[4] recommend the use of the 75-g OGTT. The ADA recommends either a one-step procedure with the OGTT (75-g or 100-g) or a two-step procedure using a 50-g glucose challenge test (GCT) followed by an OGTT.[1] The ASGODIP recommends a GCT for low-risk women at the first prenatal visit and a 75-g OGTT for high-risk women.[13] The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel recommends either a fasting plasma glucose, HbA1c or random plasma glucose at the initial visit. If test results are not diagnostic, the panel[24] recommends doing a 75-g OGTT at 24 to 28 weeks of gestation.

The NICE[25] no longer recommends using the GCT. It reviewed the use of the 50-g GCT in 4 studies involving 2437 women. The qualitative strength of the GCT as a screening tool is only fair with a calculated positive likelihood ratio of 4.34 (95%CI 1.53-12.26) and a negative likelihood ratio of 0.42 (95% CI 0.33-0.55). A local study showed that the 50-g GCT had a positive predictive value of 44.6%. The 50-g GCT is also only moderately reproducible[26], more likely to be positive if conducted in the afternoon[27], and the results are significantly affected by the time since the last meal.[28]

A one-step approach using the OGTT is recommended as 10%[5] to 23%[29] of women fail to return for an OGTT after an initial GCT. Locally, in a study[30] which used a two-step approach to screen for GDM, 36% of the women failed to return for the diagnostic OGTT after a positive GCT result. In the ASGODIP data, two hospitals reported that 17.8%[31] and 48%[32] of women with positive GCT results failed to return for OGTT.

The 75-g OGTT appears to have a slight advantage in two small trials that directly compared outcomes of women diagnosed with gestational diabetes using the 75-g vs the 100-g OGTT. Pettitt et al compared the utility of the 75-g vs the 100 g OGTT in predicting macrosomia and cesarean section in Pima Indians.[33] There were 5 discrepant results and in each case, the 75-g OGTT result was abnormal while the 100-g was not. In a study conducted in Thailand, it was demonstrated that of 14 women who delivered macrosomic infants, 6 women had abnormal 75-g OGTT test results while only 3 had abnormal 100-g OGTT results.[34]

The 100-g OGTT is more cumbersome, with blood samples taken at 4 time points, a duration of 3 hours and with a high glucose load that is often unpalatable to pregnant women. Furthermore, the 75-g OGTT has been the international standard for the diagnosis of diabetes in non-pregnant adults and it use in pregnancy would allow direct comparison with the postpartum OGTT.

Issue 6.4 What criteria will be used to interpret the 75-g OGTT?

The criteria put forth by the International Association of Diabetes & Pregnancy Study Groups (IADPSG) will be used to interpret the 75-g OGTT (Grade B, Level 3).

Summary of Evidence:

There are several ways by which the 75-g OGTT has been used to diagnose gestational diabetes (Table 3). The IADPSG recommendations[24] have the advantage of having been based on an analysis of the HAPO study[35] results which enrolled an "ethnically diverse cohort of ~25,000 women in the third trimester of gestation." Blood glucose levels at which odds ratios for specific outcomes reached predefined values were used to determine the recommended thresholds.

Table 5. Interpreting the 75-g OGTT Results

75-g OGTT	Threshold(s) for diagnosing gestational diabetes (mg/dL)			
	IADPSG*	ADA**	ASGODIP & DIPSI	POGS*
FBS	92	95	NA	92
1-hour	180	180	NA	NA
2-hour	153	155	140	NA
3-hour	NA	140	NA	140

* Any one value meeting threshold is considered gestational diabetes.
** Two values must meet thresholds to be considered gestational diabetes.

Legend: IADPSG: International Association of Diabetes and Pregnancy Study group
ADA: American Diabetes association
POGS: Philippine Obstetrics and Gynecology Society
ASGODIP: AFES Study Group on Diabetes in Pregnancy

Issue 6.5 Can we use other tests to screen pregnant women for diabetes?

The following tests should not be used for the diagnosis of diabetes in pregnancy: FBS alone, Capillary Blood Glucose, RBS, HbA1c, Fructosamine, Urine Glucose

However, if patients already have RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals, while FBS should be interpreted based on the IADPSG cut-off 92 mg/dL, with levels lower than 92 warranting 75-gram OGTT. Those with glucosuria, elevated CBG or HbA1c should undergo OGTT.

Summary of Evidence:

Though glucose meters sample whole blood, the amount of glucose is measured in the plasma ultrafiltrate. During fasting state, capillary and venous blood glucose values are not significantly different. In the postprandial state, these concentrations are different, with glucose being higher in capillary than venous blood.

Few studies have been done to determine the value of capillary blood glucose testing in the diagnosis of GDM, compared with either the 75G OGTT and 100G OGTT. Different glucose meters were used as well. Based on 2 small population-based studies (GDM n=196 and 55), sensitivity of this test ranged from 47 - 87% while specificity ranged from 51-100%. These data imply a lack of precision in using these instruments. The validity of capillary blood glucose testing to screen for GDM remains to be proven.[36-39]

The ideal screening test for diabetes during pregnancy should be one in which the results would vary very little throughout gestation. The data on changes in FBS throughout gestation are inconsistent, showing different values with advancing gestation among normal pregnant women. There is paucity of data regarding the reproducibility of FBS among pregnant women.[40-42]

The utility of random blood glucose compared with glucose tolerance testing was done on pregnant women in two studies but the design and analysis of these two studies made the interpretation of the results difficult. In the second study, both studies employed multiple random blood glucose results for their calculations; in the first, a mean of five values taken on a single day during the third trimester, and in the second, the highest of random samples taken throughout pregnancy, the highest sensitivity (75%) was obtained at a random blood glucose of 6.5 mmol/L (117 mg/dL). The corresponding specificity was 78%.[43-44] Currently, there is an inadequate amount of data available to support the use of random glucose testing as a screening test for GDM.

HbA1c has been evaluated as a possible screening test for GDM. Results showed that A1c in normal pregnant women vary with ethnicity and with gestational age. The distribution of values of HbA1c was found to be no different between women who did and those who did not have GDM making it a poor screening test.[45-46]

Fructosamine has been examined as a potential screening test for GDM. As with HbA1c, fructosamine concentrations vary with gestational age and prevailing albumin levels. Fructosamine concentrations were also found to be no different among those with and without GDM.[47-48]

Urine testing is a poor screening instrument especially among pregnant individuals. Several observational and retrospective studies have shown that glucosuria (defined as trace glucose of 75 to >250 mg/dL) showed low sensitivity ranging from 7-36%. Specificity was high ranging from 83-98%.

Given that pregnant patients are frequently advised to take vitamins, it would be prudent to note that high ascorbic acid intake can also cause glucosuria. High levels of urinary ketones such as in starvation ketosis can produce false positive glucosuria.[49-53]

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Issue 6.6 How should we follow up women who develop diabetes during pregnancy?

Postpartum recommendation. A 75-gram oral glucose tolerance test should be done 6–12 weeks after delivery in GDM women who do not have diabetes immediately postpartum. (Grade D, Level 4-5)

An FBS or RBS is not recommended for the long term follow-up and reclassification of women with previous GDM. (Grade C, Level 4). However, if patients already have FBS or RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals. [Grade D, Level 4-5]

Table 6. Metabolic assessments recommended after GDM

Time	Test	Purpose
Post-delivery (1-3 days)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early post-partum (around the time of post-partum visit)	75 –gm 2-hr OGTT*	Post=partum classification of glucose metabolism**
1 –year post-partum	75 –gm 2-hr OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Tri-annually	75 –gm 2-hr OGTT	Assess glucose metabolism
Pre-pregnancy	75 –gm 2-hr OGTT	Classify glucose metabolism

* OGTT Oral glucose tolerance test
** Classification of glucose metabolism by criteria recommended by the ADA

Summary of Evidence:

It is very important to do laboratory testing or retesting after delivery to identify glucose intolerance among women with GDM. After GDM, 35–60% of women develop type 2 diabetes within 10 years. Identification of abnormalities in glucose metabolism allows the initiation of strategies for primary prevention of diabetes.

The guidelines reviewed all recommend that retesting after GDM should be done within 6-12 weeks after delivery. The 5th International GDM workshop, the ADA 2009 and the Diabetes in Pregnancy study group of India all recommend that retesting be done using the 75-gm OGTT. The NICE however, recommends that an FBS should be done within 6 weeks after delivery.

Several studies have shown that measuring only the fasting plasma glucose level postpartum is not sufficiently sensitive to identify all women who have IGT or type 2 diabetes. Post partum data indicates that only 34% of the women with IGT or type 2 diabetes had impaired fasting glucose and that 44% of those with type 2 diabetes had fasting levels <100 mg/day (<5.5 mmol/l).

Status of glucose metabolism should be assessed periodically with an 75-gram oral glucose tolerance test. Fasting plasma glucose alone has low sensitivity of to detect IGT and diabetes. Large population studies have not established an optimum testing frequency or evaluated modified testing strategies based on risk factors. Without such data, it is recommended that after initial postpartum testing, an oral glucose tolerance test should be repeated in 1 year and, at a minimum, every 3 years thereafter.

GDM identifies women at high risk for diabetes representing a unique opportunity and a responsibility to educate the patient and health care system for primary diabetes prevention. Lifestyle change and use of metformin or thiazolidinediones (rosiglitazone and pioglitazone) can prevent or delay the progression of IGT to type 2 diabetes after GDM.

Women with previous GDM should also undergo screening for other cardiovascular risk factors and components of metabolic syndrome. (Grade D, Level 4-5)

Summary of Evidence:

Many women with prior GDM exhibit characteristics of the metabolic syndrome (e.g., glucose intolerance, insulin resistance, central obesity, elevated triglycerides, and low HDL cholesterol) and inflammatory markers (e.g., high-sensitivity C-reactive protein and interleukin-6). They may manifest short-term endothelial dysfunction during late pregnancy that is manifested as transient hypertension. Long-term endothelial dysfunction may be associated later in life with increased risk of chronic hypertension and CVD.

Insulin resistance may be implicated in transient hypertension and has been associated with inflammatory responses. Chronic insulin resistance may produce chronic inflammation, adversely affecting vascular reactivity and atherogenesis, and set up future hypertension and ischemic vascular disease in these women. Standard screening guidelines for CVD risk factor assessment should be followed at the times that glucose metabolism is evaluated.

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Summary of Recommendations: Screening and Diagnosis of Gestational Diabetes Mellitus (GDM)

- All pregnant women should be screened for gestational diabetes (Grade B, Level 2).
- All pregnant women should be evaluated at the first prenatal visit for risk factors for diabetes (Grade C, Level 4).
  - Prior history of GDM
  - Glucosuria
  - Family history of diabetes
  - First-degree relative with type 2 diabetes
  - Prior macrosomic baby
  - Age >25 years old
  - Diagnosis of polycystic ovary syndrome
  - Overweight/obese before pregnancy
  - Macrosomia in current pregnancy
  - Polyhydraminos in current pregnancy
  - Intake of drugs affecting carbohydrate metabolism
- High-risk women should be screened at the soonest possible time (Grade B, Level 3).
- Routine testing for gestational diabetes is recommended at 24 to 28 weeks age of gestation for women with no risk factors (Grade B, Level 3).
- Testing for gestational diabetes should still be carried out in women at risk, even beyond 24 to 28 weeks age of gestation (Grade C, Level 3).
- An oral glucose tolerance test (OGTT), preferably the 75-g OGTT, should be used to screen for gestational diabetes (Grade B, Level 3).
- The criteria of the International Association of Diabetes & Pregnancy Study Groups (IADPSG) should be used to interpret the 75-g OGTT(Grade B, Level 3) **where any one value meeting threshold is considered gestational diabetes.**
- The following tests should not be used for the diagnosis of diabetes in pregnancy: FBS alone, RBS, Capillary Blood Glucose, HbA1c, Fructosamine, Urine Glucose
- However, if patients already have RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals, while FBS should be interpreted based on the IADPSG cut-off 92 mg/dL, with levels lower than 92 mg/dL warranting 75-gram OGTT. Those with glucosuria, elevated CBG or HbA1c should undergo OGTT.

Summary of Recommendations: Postpartum recommendations for GDM

- A 75-gram oral glucose tolerance test should be done 6–12 weeks after delivery in GDM women who do not have diabetes immediately postpartum. (Grade D, Level 4-5)
- An FBS or RBS is not recommended for the long term follow-up and reclassification of women with previous GDM. (Grade C, Level 4). However, if patients already have FBS or RBS at the time of consultation, thresholds used for non-pregnant patients should be used.
- **Women with previous GDM should also undergo screening for other cardiovascular risk factors and components of metabolic syndrome. (Grade D, Level 4-5)**

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Philippine PRACTICE GUIDELINES FOR DIABETES MELLITUS Part 2:

OPD MANAGEMENT OF TYPE 2 DIABETES MELLITUS

The methodology and framework for the development of the clinical practice guidelines has been discussed in part 1 (Screening and Diagnosis).

The UNITE for DM CPG used the Oxford Centre for Evidence-Based Medicine Levels of Evidence (March 2009) for grading the levels of the evidence and the strength of recommendations (Appendix D: CEBM Levels of Evidence and Strength of Recommendation). Briefly, the levels of the evidence are graded according to Arabic numerals 1-5, considering the hierarchy of literature (e.g., for questions of therapeutic efficacy, randomized controlled trials are ranked higher than non-blinded or non-randomized trials or observational studies).

The strength of the guideline recommendation is indicated by the letters A to D as follows:

- Grade A is the strongest recommendation based on consistent level 1 studies (**strong recommendation** to use or not to use an intervention or test);
- Grade B strength is derived from consistent level 2 or 3 studies or extrapolations from level 1 studies (**moderately strong recommendation**);
- Grade C strength is from level 4 studies or extrapolations from level 2 or 3 studies (**intermediate strength of recommendation**); and
- Grade D is based on level 5 evidence or troublingly inconsistent or inconclusive studies of any level (**weak recommendation**).

This second set of guidelines focus on the outpatient management of Type 2 diabetes mellitus.

Question 1. How is diabetes care delivered in the Philippines? How is diabetes care organized?

1.1 Organization of diabetes care in the Philippines - In the Philippines, there are several clinical settings where diabetes screening, education and management can be organized and delivered. For example, at the level of the barangay health station (BHS), the health worker should have the capability to deliver diabetes self-management education, do blood pressure and weight/BMI monitoring but it will be at the level of the RHU/City or Provincial Health Office where diabetes clubs will be encouraged to be set up. At all levels of health care, education and training will be done so that health care workers will have the competencies needed for health education, screening and management

The strategy will be patient-empowerment; the team should be centered on the person with diabetes focusing on self-management

1.2 Who comprises the diabetes team? In the hospital setting, the diabetes team can be composed of an organized multidisciplinary organization: Nurses, pharmacists, diabetes educator, dietitian and dentist, with the physician (general physician or a diabetes specialist) as the head of the team; others: exercise specialist, mental health professional (psychologists, psychiatrists, mental health nurses). In the local health centers (RHU/CHO/BHS), the midwife, primary health nurse or barangay health workers with adequate training in diabetes education, can serve as the diabetes educators. Lay health workers or patients who have been instructed on various aspects of diabetes may also deliver DSME under the supervision of the clinic doctor.

Question 2. What should be done during the initial evaluation of a diabetic patient?

2.1 The **initial evaluation** of the diabetic patient should include a comprehensive medical history (Table 1) and physical examination (Table 2).

Table 1. Diabetes Care Checklist (Medical History)

The following points should be elicited in the initial medical history

- Age and characteristics of onset of diabetes (e.g., history of Diabetic ketoacidosis, asymptomatic laboratory finding)
- Nutritional status and weight history
- Growth and development in children and adolescents
- History of Smoking
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes: medications, meal plan or eating patterns; physical activity patterns, and; results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycemic episodes and risk for hypoglycemia
- Hypoglycemia awareness
- Any severe hypoglycemia: frequency and cause
- Symptoms or history of diabetes-related complications:
  - Microvascular: retinopathy, nephropathy, neuropathy, autonomic, including sexual dysfuction and gastroparesis
  - Macrovascular: stroke, coronary artery disease, peripheral vascular disease
- Others: psychosocial problems, dental disease

2.2 The comprehensive initial evaluation should include the following tests (Table 2):

Table 2. Diabetes Care Checklist (Physical Examination)

- Height, weight, BMI, waist circumference
- Blood pressure determination, including orthostatic measurements when indicated
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination
  - Inspection,
  - Palpation of dorsalis pedis and posterior tibial pulses,
  - Presence/absence of patellar and Achilles reflexes,
  - Determination of proprioception, vibration, and monofilament sensation
- Tests for autonomic dysfunction
- Testing for heart rate variability, if indicated, which may include expiration-to-inspiration ratio and response to the Valsalva maneuver and standing.
- Fundoscopic examination
- Thyroid palpation

Recommendation 2.2.1 - Cardiovascular Risk Assessment. Determining the coronary heart disease risk factors (history, BP, BMI, WC) on initial consultation or follow up helps determine the patient's risk for further complications and thus, appropriate steps could be done to address these risks. (Grade A, Level 1)

The initial and ongoing assessment of people with diabetes should include weight and height measurements and calculation of the BMI (kg/m^2), and waist circumference (WC) to assess the degree of abdominal fat.

Table 3. Classification of Overweight and Obesity by Various Reference Groups

Anthropometric measures	WHO Asians[2]	WHO[1-2]
BMI Overweight	23 (kg/m^2)	25 (kg/m^2)
BMI Obese	25 (kg/m^2)	30 (kg/m^2)
WC cutoff value	90 cm in men 80 cm in women	101.6 cm in men 88.9 cm in women

BMI- Body Mass Index; WC = waist circumference

1. WHO Expert Consultation. Lancet. 2004;363:157-163;
2. International Diabetes Institute. The Asia-Pacific perspective: Redefining obesity and its treatment. 2000. http://www.diabetes.come.au/pdf/obesity.report.pdf/ Accessed November 9 2011;

Recommendation 2.2.2 - Foot Evaluation.

A diabetic's risk for developing a foot ulcer may be as high as 25%.[3] Thus, the foot exam is an important part of the initial & ongoing evaluation of any diabetic. ***Identify risk factors for developing foot complications from the history or PE focusing on previous foot ulceration, neuropathy (loss of protective sensation), foot deformity, & vascular disease*** (Grade A, Level 1).[4]

Risk factors for diabetic foot disease include:
- Peripheral vascular disease(PVD)*
- Peripheral neuropathy
- Previous amputation
- Previous ulceration
- Presence of callus
- Joint deformity
- Visual/mobility problems.

Risk factors for PVD are smoking, hypertension and hypercholesterolemia. The cumulative effect of these risk factors for PVD is considered to be at least additive. Appropriate footwear is recognized in the literature as an important part of management to prevent diabetic foot disease.

Recommendation 2.2.3 - Eye Examination

T2DM has an insidious onset and some patients may already have retinopathy at the time of diagnosis.[5] It is suggested to have a comprehensive evaluation for retinopathy by an ophthalmologist upon diagnosing diabetes. (Grade A, Level 1)

Recommendation 2.2.4 - Dental History and Oral Health

In a local study in 192 adult patients with T2DM in SLMC, the prevalence of periodontitis among the Type 2 DM population studied was 68.23%.[6]

Patients or for children, parents should be asked about any red flags of dental disease such as tooth ache, pain when chewing, sensitivity to cold or hot drinks, presence of badly broken down teeth, swelling of the gums, and bad breath.

Ask also about manifestations of periodontitis such as bleeding on brushing teeth, swelling and redness of the gums, looseness or mobility of teeth, and teeth that fall off in adult patients.

Due to the high prevalence of dental and oral diseases among diabetics, a thorough dental history should be elicited so that appropriate referrals to dentists can be made. (Grade A, Level 1)

Summary of the Evidence:

An increasing number of studies involving type 1 and type 2 diabetics have shown that diabetic patients have an increased risk of developing caries or tooth decay and periodontal disease, the two most common diseases that affect the mouth. Tooth decay is the loss of tooth structure secondary to bacteria that utilizes available sugar in the mouth to produce acid that demineralizes the tooth and produce cavities. Periodontal disease is generally divided into gingivitis and periodontitis. Gingivitis is the inflammatory reaction of the gingiva to microorganisms in the biofilm that attaches to a tooth near the gums. It is characterized by redness, swelling, and bleeding of the gums. In Periodontitis, the inflammation extends deeper from the gingiva into the connective tissue and bone surrounding the tooth. Periodontitis is manifested by increased pockets depths, gingival recession and tooth mobility.

Dental diseases such as caries and periodontal disease can directly and indirectly affect glycemic control. Directly, both caries and periodontal disease can result in acute infection that can upset a diabetic patient's glycemic control or further increase an already high blood sugar level. Indirectly, both caries and periodontal disease can affect the patient's ability to chew due to pain or discomfort while chewing. The patient then turns to easily digestible foods that are easy to chew but are rich in sugar content.

Furthermore, some studies have shown that diabetes and periodontal disease share a common pathway in Inflammation. Inflammation arising from periodontitis can result in increased levels of inflammatory mediators that can further increase insulin resistance. Periodontitis also has been associated with increased risk for cardiovascular disease, end-stage renal disease, and pre-term and low birth weights in diabetic and non-diabetic patients.

Recommendation 2.2.5 - Evaluation of the Thyroid Gland

Although thyroid disease is reported to be relatively

common in type 1 diabetes, a longitudinal Australian study in type 2 diabetic women without known thyroid disease showed that sub-clinical hypothyroidism is a common, but incidental finding.[7] Increased risk for thyroid autoimmunity in adult type 2 diabetic patients with GAD65 autoantibodies has been reported, and these findings have been confirmed in paediatric populations.[8,9]

The prevalence of sub-clinical hypothyroidism is also higher in patients with metabolic syndrome than those without it.[10]

It is suggested that screening for thyroid disease be done among patients with signs and symptoms of metabolic syndrome or when an autoimmune etiology is suspected. (Grade C, Level 3)

2.3 What laboratory tests should be requested during the initial consultation?

Minimal Tests:

The following tests are suggested to be done routinely for all individuals being seen for the first time for evaluation of diabetes.

- Fasting blood glucose and lipid profile, including total, LDL and HDL cholesterol and triglycerides
- HbA1C
- Liver enzyme/transaminase tests (AST/ALT)

Optional Tests:

The following additional tests may be requested as indicated

- Electrocardiogram (Resting) and Treadmill Exercise Tests
- Thyroid-stimulating hormone in type 1 diabetes, dyslipidemia, or women over age 50 y

Summary of the Evidence and Rationale for recommendations:

Modifiable risk factors for coronary heart disease were identified in a cohort of over 3000 type 2 diabetics from the United Kingdom Prospective Diabetes Study (UKPDS 23). Estimated hazard ratios from this study for the upper third relative to the lower third were 2.3 for serum LDL cholesterol, 0.6 for serum high-density-lipoprotein (HDL) cholesterol, 1.5 for hemoglobin A1C, 1.8 for systolic blood pressure, and 1.4 for smokers.[11]

Glycosylated hemoglobin HbA1c or A1c is a known predictor for different complications related to diabetes and can give a gauge as to the duration of the patient's hyperglycemia. Even at baseline, it is highly recommended that this measure should be obtained among suspected diabetics (Grade A, Level 1).

Screening for microalbuminuria should begin at diagnosis in patients with type 2 diabetes because many have had diabetes for several years before diagnosis. The CANDI-Manila showed that as much as 42% of newly diagnosed Filipino diabetics has proteinuria by routine urinalysis.[12]

Individuals with type 2 diabetes have a higher incidence of transaminase abnormalities than individuals who do not have diabetes. The most common abnormality is elevated ALT. Determination of transaminases in patients with type 2 diabetes should occur at the start of drug therapy and if patients have risks for raising concern about hepatic impairment (Grade B, Level 2).

CAD risk factors identified by the American Diabetes Association (dyslipidemia, hypertension, smoking, positive family history of early coronary disease, and presence of micro- or macroalbuminuria) do not predict the likelihood of having ischemic findings on stress testing or coronary angiography.[13] Therefore, this guideline consistent with the ADA does NOT recommend screening "high risk" diabetic patients with cardiac stress testing. Candidates for screening with stress testing are patients with a history of peripheral or carotid arterial disease and those over age 35 who have a sedentary lifestyle and are planning to begin a vigorous exercise program (Grade C, Level 3).

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Question 3: What are the elements of diabetes self management education?

Recommendations for Diabetes Self Management Education

Who (should receive DSME): DSME should be offered to all diabetic patients, their carers and family (Diabetes care should be organized around the person with diabetes using a multi- and interdisciplinary team approach centered on self-care management) (Grade B, Level 2-3)

When: Ideally, newly diagnosed patients or those who have not had the benefit of undergoing diabetes education, or patients who require reinforcement should

receive DSME. However, it should not be time-limited but should be ongoing and can be delivered any time during the diabetes course whenever the health professional sees the need for reinforcement. (Grade D, Consensus)

How: Using a structured, evidence-based individualized program combined with group education (within the context of diabetes clubs). Supporting materials such as reading materials, pamphlets, video or slides should be provided to reinforce learning. (Grade B, Level 2)

What: Areas/aspects of DSME: self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers including problem-solving, goal-setting and active participation in decision-making. (Grade D, consensus)

What should be taught:
(1) interpreting and acting on the results of self-monitoring of blood glucose;
(2) making informed management decisions about insulin, medications, nutrition, physical activity and other lifestyle (cigarette smoking) issues; and
(3) daily preventive practices such as foot care, exercise
(4) Targets for CV risks –BP, lipids
(5) Sick day management

Who should deliver DSME? Any member of the diabetes health team who has adequate training can deliver DSME with the physician as the head of the team and coordinator. This team can include the diabetes educator, dentist, nurse, pharmacist and nutritionist/ dietitian. [Grade B, Level 2]

- In the local health centers, the midwife/nurse or barangay health worker with adequate training in diabetes education, can serve as the diabetes educator
- Lay health workers or patients who have been instructed on various aspects of diabetes may also deliver DSME under the supervision of the clinic doctor.

Question 4. What are the targets for glycemic control?

4.1 What is the rationale for controlling blood sugar? Why should we control blood sugar?

Optimal glycemic control is fundamental to the management of diabetes. There is compelling evidence that improved glycemic control reduces risks of development and/ or progression of microvascular complications in type 2 diabetes. (Level 1, Grade A)

The effect of intensive glycemic control on macrovascular outcomes is also confirmed, although more modest, compared to its benefit on onset or progression of microvascular complications.

Summary of the evidence: Glycemic control is proven to decrease microvascular disease complications and to have a modest benefit on the long term prevention of cardiovascular diseases.

All the guidelines reviewed agree on the importance of glycemic control. The data from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a continuous relationship between A1C and diabetes complications, with no apparent glycemic threshold for benefit.[1-3] Epidemiological analyses of the DCCT and UKPDS suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair or good control.

Follow up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study and of the UKPDS cohorts has shown persistence of these microvascular benefits in previously intensively treated subjects, even though their glycemic control has been equivalent to that of previous standard arm subjects during follow-up.[4-6]

These analyses also suggest that further lowering of A1C from 7 to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller. In the UKPDS, microvascular endpoints (including retinopathy and nephropathy) decreased by 37% with each 1% absolute reduction in HbA1c, with no threshold observed.[2,3] This suggests that any reduction in average HbA1c is likely to reduce the risk of complications, with the lowest risk being in those with average HbA1c levels less than 6%. There is less evidence demonstrating that improved glycaemic control reduces the risk of macrovascular complications of diabetes. However, the risk of macrovascular complications of diabetes is associated with the level of hyperglycaemia.

Improvements in glycaemic control are associated with improvements in quality of life, providing there is no increase in hypoglycaemic symptoms.[7] One of the drawbacks of tight glycemic control includes more frequent hypoglycaemic episodes. Severe hypoglycaemia may adversely affect quality of life in people with diabetes treated with insulin, particularly newly diagnosed people with diabetes.[8] It also predisposes to cardiovascular events in susceptible individuals as seen in the ACCORD and VADT trials where tight glycemic control aiming for HBA1c of <6.0% in elderly patients with long-standing diabetes led to more cardiovascular events.[9,10]

Drugs used for managing diabetes may also promote weight gain.[2,3] This adverse effect of intensifying treatment should be part of considerations for choice of therapy.

4.2 What should we monitor and target?

4.2.1 The ideal target is the HbA1c; HbA1c should be measured using a National Glycosylated Hemoglobin Standardization Program certified method and results should be DCCT-aligned. (Level 1, Grade A)

4.2.2 Measure the individual's HbA1c levels at 3–6-monthly intervals tailored according to individual needs and access to laboratory facilities. (Level 1, Grade A)

HbA1c monitoring may be inaccurate/ invalid in the following conditions because of disturbed erythrocyte turnover or abnormal haemoglobin type: pregnancy, hemolysis, blood loss and hemoglobinopathies.[6] Use appropriate alternative measures such as quality-controlled plasma glucose profiles, total glycated hemoglobin estimation or fructosamine estimation where HbA1c methods are invalid.

4.2.3 If HbA1c levels remain above target levels, but

pre-meal self-monitoring levels remain well controlled (<7.0 mmol/litre or 126 mg/dL), consider self-monitoring to detect postprandial hyperglycaemia (>8.5 mmol/litre or 150 mg/dL) and manage to below this level if detected.

4.3 What are some of the other methods for monitoring glycemic control

4.3.1 **FBS, RBS**. Where and when HBA1c determination is not possible or may be invalid, or when short term control of blood sugar is to be assessed, alternative measures to monitor glycemic control include fasting blood glucose and prostprandial blood glucose. Estimated trends in blood glucose control may be obtained using quality-controlled plasma glucose profiles. (Level 3, Grade C)

4.3.2 **Capillary Testing**. Point -of-care or clinic-based capillary plasma glucose monitoring at random times of day is not generally recommended but if there are no other ways to gauge glycemic control then this may have a role. (Level 3, Grade C)

Site-of-care capillary blood glucose meters should be quality controlled by reference to laboratory methods.

4.3.3 **Colorimetric glucose strips**. The International Diabetes Federation states, under minimal standard of care, that the visually read glucose test strips have a role in emergency and remote situations where maintenance of functional meters is not feasible.

4.4 What are the targets for Glycemic control?

4.4.1 Glycemic targets must be individualized. A target A1C of <7.0% should be considered in all patients with type 2 diabetes in order to reduce microvascular complications.

In order to achieve A1C of 7.0%, people with diabetes should aim for[2]:

- An FPG or preprandial PG target of 4.0 to 7.0 mmol/L (72 to 126 mg/dl) [Grade B, Level 2[1], for type 1; Grade B, Level 2[2,3], for type 2 diabetes]; and
- A 2-hour postprandial PG target of 5.0 to 10.0 mmol/L (90 to 180 mg/dL) [Grade B, Level 2[1], for type 1 diabetes; Grade B, Level 2[2,3], for type 2 diabetes].
  - Alternatively, capilary blood glucose targets can be: FBS 90-130 mg/dL (ADA), PPBG <180 (ADA)

4.4.2 A target of <6.5% may be optimal for certain types of patients such as those with short duration of diabetes, long life expectancy, no significant active cardiovascular disease, no serious co-morbid risk factors and at low risk for cardiovascular events that may be triggered by hypoglycemia.

In order to achieve a target A1c <6.5%, the patient must achieve the following plasma glucose level:

- Fasting: <6.0 mmol/L (or <110 mg/dl)
- Postprandial: <8.0 mmol/L (or <145 mg/dl).

4.5 Who should be required to do self-monitoring of blood glucose? How frequent should SMBG be done?

The following patients should be encouraged to do self monitoring of blood glucose (SMBG):

- All patients on insulin therapy
- Patients at risk of hypoglycemia on oral therapy.

The frequency of SMBG should be determined individually. The table summarizes the recommendations from the IDF, CDA, ACE, ADA, NZGG and UK-NICE regarding frequency of capillary blood glucose monitoring:

Table 4. Frequency of and Indications for Self Monitoring of Blood Glucose

Specific Condition/ Type of Therapy	Frequency of Monitoring
Intensive Insulin therapy with 2 or more injections	*Test cbg at least 3x a day including pre and post prandial, at bedtime and when there are symptoms of hypoglycemia.* *Occasionally test at 2:00 or 3:00 AM if there are nocturnal hypoglycaemic episodes.* *Test blood sugar before driving in patients with frequent hypoglycaemic episodes.*
Once daily insulin plus oral meds with high HBA1c	*Test at least twice daily including pre and postprandial glucose*
Patients with stable diabetes	*Testing before meals and at bedtime at least one or two days a week* *AND* *Test before breakfast and 2 hours after each meal at least once or twice a week*
Newly diagnosed patients	*Test cbg as part of self-management education and instruction on how to interpret results and targets*
All type 2 DM regardless of therapy on days with sickness and when there are changes in daily physical acitvity (all)	*Check cbg at least 3x a day during intercurrent illness, or travel period*

Summary of the Evidence:

The IDF recommends that self-monitoring of blood glucose (SMBG) should be available for all newly diagnosed people with Type 2 diabetes, as an integral part of self-management education so the patient can understand its purpose, its interpretation and how it should be acted upon. Structured assessment of self-monitoring skills, the quality and use made of the results obtained, and of the equipment used, should be made annually.

The need for self blood glucose monitoring is also dependent on the degree of glycemic control and the

type of therapy the patient has. Frequent testing is an integral component of care in diabetes patients using insulin. In a large, nonrandomized study of individuals with stable type 2 diabetes using insulin, testing at least 3 times a day was associated with improved glycemic control.[14] The frequency and timing of testing should take into account the potential for hypoglycemia associated with the specific treatment regimen, and the fact that postprandial hyperglycemia is associated with increased cardiovascular risk.[15,16]

In people with higher HBA1c levels (>8.5%), it is the fasting plasma glucose that is more reflective of the hyperglycemia and treatment should be adjusted to control it.[17] Postprandial PG results are generally better correlated to A1C than tests taken at other times of the day.[17,18] Testing before and after meals is associated with improved glycemic control compared to preprandial testing alone.[19]

Patients whose glycemic levels are above target or who experience frequent hypoglycemia should monitor glucose levels more frequently both in preprandial and 2-hour postprandial states. Since nocturnal hypoglycemia may be more frequent in intensively managed individuals, periodic overnight testing occasionally at 2:00 AM to 3:00 AM to detect nocturnal hypoglycemia at a time corresponding to peak insulin action should be undertaken.[1,20–22] Glucose levels should be checked anytime there is a suspected (or risk of) low glucose level and/or before driving.[23] SMBG should also be done more often in patients with hypoglycemia unawareness.[15,16,20-22] The American College of Endocrinology states that patients whose glycemic levels are above target while being treated with oral agents with or without once daily insulin should monitor glucose levels at least 2 times daily.

A review cited by the United Kingdom National Insititutes of clinical Excellence CPG concluded that, in the short term, and when integrated with educational advice, self-monitoring of blood glucose as an adjunct to standard therapy, may contribute to improving glycaemic control among non-insulin requiring Type 2 diabetes patients.[24]

In one study, Jansen reported that interventions with SMBG were found to be more effective in reducing HbA1c than interventions without self-monitoring. The reduction in HbA1c was statistically significant and it was estimated to be around 0.4%. This effect was increased when regular feedback was added to the SMBG and was shown in both an insulin treated Type 2 diabetes group, and in a group of Type 2 diabetes patients that included those being treated with oral agents.[25] In a German retrospective cohort study, there was a reduction in both morbidity and mortality associated with SMBG in both insulin and non-insulin treated type 2 DM patients over a 6.5 year observation period.[26]

Blood glucose self-monitoring can be useful when it is used to change behaviour or medication dose, document frequency of hypoglycaemic episodes and hypoglycaemia unawareness. Testing before meals and at bed time on one or two days a week is reasonable for people with stable type 2 diabetes, although for those with controlled diabetes on medical nutrition therapy, periodic HbA1c monitoring may be sufficient.[27-29] Testing before breakfast and two hours after each meal may better facilitate achieving glycaemic or treatment goals.[19,27-29]

4.6 How soon should glycemic targets be achieved?

Ideally targets should be achieved within **six** months of diagnosis or initiation of treatment as epidemiologic evidence already shows that at the time of first diagnosis, a fourth of all patients with diabetes already have microvascular complications.

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5. What are the targets for Decreasing Global Cardiovascular Risks? Blood Pressure Targets

5.1 What are the targets for optimal blood pressure control?

The goal BP for most diabetic patients is <140/80 mm Hg. (B)[1]

Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. (C)

5.2 Lifestyle therapy for hypertension consists of weight loss if over weight, DASH-style dietary pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. (B)

5.3 When should treatment be started?

Lifestyle therapy alone can be given for 3 months for those with pre-hypertension with SBP 130-139 mm Hg or DBP 80-89 mm Hg.

Pharmacologic therapy + lifestyle therapy should be started for those with hypertension defined SBP ≥140 mm Hg or DBP ≥90 mm Hg, or pre-hypertension uncontrolled by lifestyle therapy alone

5.4 What drugs should be started for diabetics with hypertension?

ACE inhibitors & ARBs are generally recommended as initial therapy. If one class is not tolerated, the other should be substituted.

Multiple drug therapy (two or more agents at maximal doses) is generally required for diabetics to achieve blood pressure targets. (B). Thiazide type diuretics, Calcium channel blockers, and ß-blockers may be given as additional agents.

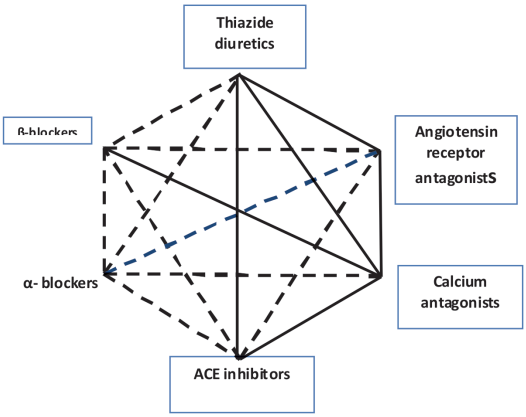

Figure 1. Possible combinations between some classes of anti-hypertensive drugs

The preferred combinations in the general hypertensive population are represented as thick lines.

The frames indicate classes of agents proven to be beneficial in controlled intervention trials

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6. Targets for Decreasing Global Cardiovascular Risks: Treatment recommendations and Goals for Diabetic Dyslipidemia

6.1 LDL is the primary target for dyslipidemia management in diabetics

6.2 Statin therapy should be added to life-style therapy, regardless of baseline lipid levels, for diabetic patients:
- with overt CVD. (A)
- without CVD who are over the age of 40 years and have one or more other CVD risk factors. (A)

6.3 For patients at lower risk (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dl or in those with multiple CVD risk factors.

6.4 Goals for Therapy: The 100-70 rule
- In individuals without overt CVD, the primary goal is an LDL cholesterol <100 mg/dl (2.6 mmol/l). (A)
- In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option. (B).

6.5 Goals for therapy: Alternative target
- If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of approx 30 – 40% from baseline is an alternative therapeutic goal. (A)

6.6 How about triglycerides and HDL-cholesterol?

Triglyceride levels <150 mg/dl (1.7 mmol/l) and HDL cholesterol >40 mg/dl (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women, are desirable. However, LDL cholesterol- targeted statin therapy remains the preferred strategy. (C)

If targets are not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid- lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety. (E)

7. Targets for Decreasing Global Cardiovascular Risks: Aspirin Use

Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men >50 years of age or women >60 years of age who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (C)

There is no sufficient evidence to recommend aspirin for primary prevention in lower risk individuals, such as men <50 years of age or women <60 years of age without other major risk factors. For patients in these age-groups with multiple other risk factors, clinical judgment is required. (C)

How about combination anti-platelets? Combination therapy of ASA (75–162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after an acute coronary syndrome. (B)

8. Targets for Decreasing Global Cardiovascular Risks: Weight Management

The initial and ongoing assessment of people with diabetes should include weight and height measurements and calculation of the BMI (kg/m^2), and waist circumference to assess the degree of abdominal fat.

An ideal body weight or BMI should be maintained whenever possible as cardiovascular risk is lowest when the BMI is normal (<23 kg/m^2) following the Asia-Pacific guidelines.

What is the recommended rate of weight loss? Target, for people who are overweight, an initial body weight loss of 5–10%, while remembering that lesser degrees of weight loss may still be of benefit, and that larger degrees of weight loss in the longer term will be advantageous (NICE).

A healthy target could be 0.5-1 kg (1-2 lbs)/wk.

Caloric restriction, independent of weight loss, improves glycaemic control within days of initiation and decreases fasting plasma glucose, free fatty acids and triglyceride levels, hepatic glucose production and increases insulin sensitivity and insulin secretion (NZ Guidelines).

9. THERAPEUTIC LIFESTYLE CHANGE: Medical Nutrition Therapy, Alcohol & Smoking

9.1 Medical Nutrition Therapy (MNT)

9.1.1 Who should receive medical nutrition therapy?

Recommendation*:* All individuals at risk for diabetes, those with prediabetes or diabetes and overweight individuals with Metabolic Syndrome should be advised regarding MNT to help attain treatment targets (Level 1, Grade A).

The American Diabetes Association recommends MNT to help achieve treatment goals for glucose, lipids and blood pressure, and to prevent or delay chronic complications of diabetes. Pastors et al. reviewed the evidence for the effectiveness of medical nutrition therapy in diabetes management. The UK Prospective Diabetes Study (UKPDS) was the largest of three randomized controlled trials which compared nutrition intervention to usual care. In the UKPDS, HbA1c decreased 1.9% (8.9 to 7%) in patients who received intensive nutrition therapy before randomization. The review also identified three meta-analyses, which showed that MNT had significant effects on weight loss and metabolic control.

9.1.2 How should counseling for medical nutrition therapy be carried out?

Recommendation*:* MNT should preferably be provided by a registered dietitian/nutritionist or other health care professional trained in the principles of nutrition (Level 1, Grade A). The scope and manner of delivery of MNT will depend on the setting.

The Canadian Diabetes Association suggests that counseling for MNT be given by a registered dietitian with competency in diabetes management. Such counseling sessions can either be individual or in small groups. In the UKPDS3, a significant reduction in HbA1c was seen in the participants who were given dietary counseling by a dietitian on study entry.

The International Diabetes Federation recommends that counseling be offered upon or shortly after diagnosis, with an initial consultation and two or three subsequent follow-up sessions. Franz et al. randomized 179 individuals with type 2 diabetes to receive usual nutrition care (one visit) or intensive nutrition intervention (at least three visits with a dietitian). Those randomized to more intensive intervention had a significant HbA1c reduction of 1-2%.

Furthermore, the IDF proposes that MNT can also be incorporated in a broader diabetes self-management education program. Sadur et al. randomized 185 individuals with type 2 diabetes in a health maintenance organization to cluster-visits with a multidisciplinary team (dietitian, nurse, psychologist, pharmacist) or usual care by a primary care physician. Those randomized to the multidisciplinary approach had an HbA1c reduction of 1.3% vs 0.2% for usual care.

The scope and manner of delivery of MNT (medical nutrition therapy) will depend on the setting.

9.1.3 In the Barangay Health Station (BHS), the following

simple nutrition messages are to be emphasized:

a. **Food choices:** Misconceptions such as skipping meals and completely avoiding rice, sugar or fruit should be addressed.

The Asian-Pacific Type 2 Diabetes Policy Group has outlined the following simple reminders:

EAT MOST
Use one or more of these foods as the basis of every meal
Vegetables, legumes, lentils, noodles, rice, bread, grains, barley, wholegrain cereals, fresh fruit (non-sweet)

Note that many sauces and preservatives that are added to these foods are high in salt, sugar or fat, and should be avoided.

EAT MODERATELY
Have small servings of protein-rich foods e.g., fish, seafood, eggs, lean meat, skinless chicken, low-fat cheese, low-fat yoghurt, low-fat milk, nuts

EAT LEAST
Minimise fats, sugars, salt and alcohol e.g., butter, oil, cream, coconut milk and cream, processed meat, fried foods, preserved or processed foods, pastries, sweets, biscuits, soft drink

b. **Idaho Plate method:**[12] It helps the patient visualize how different foods can be proportionally arranged on a plate for different meals. This method provides 1,200-1,500 calories.

9.1.4 Hospital-based nutrition advice should include the following:

a. Calculation of caloric requirements and macronutrient distribution

The Asian-Pacific Type 2 Diabetes Policy Group11 recommends the following macronutrient proportions (of total energy intake) -

Fat: no more than 30% (saturated fat <10%)
Carbohydrate: 50-55% (sucrose <10%)
Protein: 15-20%

It also recommends that salt intake be reduced to <6 g/day (NaCl) especially for those with hypertension.
The Canadian Diabetes Association[7] recommends higher intakes of dietary fiber (25-50 g/day) for individuals with diabetes.

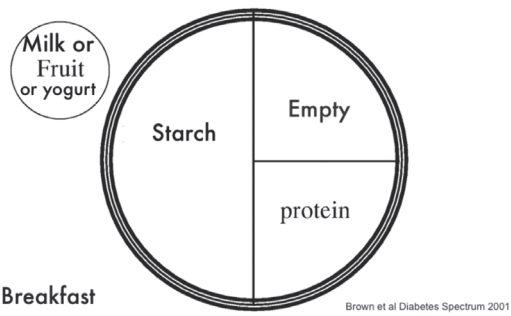

Figure 2. Idaho Plate Method - Plate for breakfast

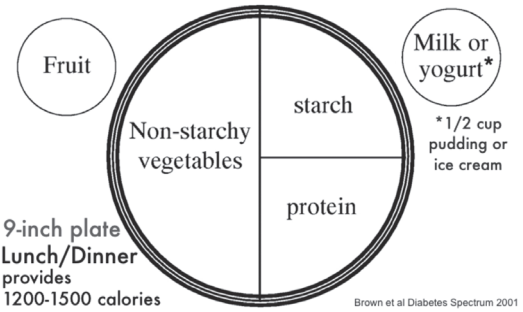

Figure 3. Idaho Plate Method - Plate for lunch or dinner

b. Exchanges or carbohydrate counting

The American Diabetes Association[1] recommends either carbohydrate counting or exchanges to monitor carbohydrate intake as dietary carbohydrate determines postprandial glucose levels.

c. How to read food labels

d. Glycemic index (GI)

The Canadian Diabetes Association[7] advises individuals with diabetes to choose low-GI foods (instead of high-GI foods) within the same food category to help reduce HbA1c. The benefits of low-GI vs high-GI diets appear to be modest. In two meta-analyses by Brand-Miller et al. and Opperman et al., low-GI diets reduced HbA1c by 0.43% (CI 0.72-0.13) and 0.27% (95% CI -0.5, -0.03) respectively, vs high-GI diets.

e. Meal replacement

Prepackaged meal replacements limit caloric intake. Use of these products once or twice daily to replace regular meals can lead to significant weight loss in overweight individuals.

9.2 Are sucrose and sucrose-containing foods allowed?

Recommendation*:* Individuals with diabetes need not avoid sucrose or table sugar as small amounts do not adversely affect glycemic control (Level 3, Grade B). Table sugar when consumed, should however replace other carbohydrate in the meal plan.

In a small 6-week cross-over study by Cooper PL et al., addition of 28 g of sucrose (roughly 2 tablespoons) to the diet of individuals with type 2 diabetes, did not have significant effects on the fasting plasma glucose.

9.3 Are sugar alcohols and nonnutritive sweeteners safe?

Recommendation*:* Xylitol, sorbitol, saccharin, aspartame, cyclamate and sucralose in the quantities usually consumed are allowed in the diet of individuals with diabetes as these have negligible effects on postprandial blood glucose (Level 3, Grade B).

In a small double-blind cross-over study of a single

high oral dose of sucralose in individuals with type 1 or type 2 diabetes, it did not appear to significantly affect plasma glucose.

9.4 Is vitamin supplementation needed?

Recommendation*:* Routine supplementation with vitamin E and C or carotene as antioxidants or chromium is not advised (Level 1, Grade A).

In the Heart Outcomes Prevention Evaluation (HOPE) trial and its extension HOPE-TOO, a daily dose of 400 IU of vitamin E in individuals with diabetes did not prevent major cardiovascular events and may increase the risk for heart failure over 7 years.

9.5 Is alcohol intake allowed?

Recommendation*:* Avoid alcohol intake. Advise caution as alcohol may cause hypoglycemia in those taking sulfonylureas or insulin, especially when taken without food.

Should adults with diabetes decide to imbibe alcohol, the American Diabetes Association[1] recommends that daily intake be limited to one drink per day or less for women and two drinks per day or less for men. The Asian-Pacific Type 2 Diabetes Policy Group[11] defines a standard drink as containing 10 g of alcohol: 285 mL beer, 375 mL light beer, 100 mL wine or 30 mL spirits).

9.6 Smoking

Recommendation*:* Advise all individuals with diabetes not to smoke (Level 1, Grade A). Refer those who smoke to smoking cessation programs.

10. THERAPEUTIC LIFESTYLE CHANGE: Physical Activity

10.1 General recommendations:

10.1.1 People with Type 2 DM should undertake aerobic physical activity at least 150 min per week, of moderate to vigorous intensity, spread out 3 days over the week with no more than 2 consecutive days between bouts of activity.

10.1.2 Moderate to vigorous resistance training at least 2-3 days a week should be undertaken by persons with T2DM

10.2 Definitions

10.2.1. **Definition of Aerobic Exercise:** Rhythmic, repeated and continuous movement of the same large muscle groups for at least 10 minutes at a time.

10.2.2 **Definition of Resistance Exercise:** Activities that use muscular strength to move a weight or work against a resistant load. Examples: Exercise with weight machines, weight lifting

Intensity of Physical Activity

10.2.3 **Moderate physical activity** means activities with energy expenditure of 3 to 6 METs. People who perform activities of this intensity for 30 minutes per day will meet the recommendations for cardiovascular benefit.

10.2.4 **Moderate Intensity** should result to an increase of heart rate to 50-70% of the maximum HR (220- age), examples: Biking, brisk walking, continuous swimming, dancing, raking leaves, Water aerobics

10.2.5 **Vigorous physical activity** means activities with energy expenditures of greater than 7 METs

10.2.6 **Vigorous Intensity:** >70% of person's maximum HR Examples: brisk walking up an incline, jogging, aerobics, hockey, basketball, fast dancing, fast swimming

10.3 Precautions during Exercise

10.3.1 Persons with T2DM may undergo physical activity with caution when BG is >300 mg/dl without ketosis as long as they feel well with adequate hydration ensured.

10.3.2 Persons on insulin and insulin secretagogues should take CHO supplement as needed to prevent hypoglycemia during and after exercise.

10.3.3 Intake of beta-blockers, diuretics and statins should be noted and corresponding precautionary measures be undertaken.

10.3.4 Individuals with long-term complications of diabetes may undergo supervised physical activity. Depending on the complication present, there are specific recommendations for screening and appropriate physical activity program designed individually.

10.4 Pre-exercise Assessment/Evaluation may include :

- ECG, Stress Testing
- Screening for CAN (CV autonomic neuropathy): battery of autonomic tests like HR variability

11. How should diabetes mellitus be treated in the outpatient (Pharmacologic Therapy)

a. Among the newly diagnosed diabetics, classify the level of severity of the diabetes according to the glycemic levels, presence of symptoms and complications

- Those who are asymptomatic with relatively lower levels of blood sugar (HbAc <8.0%, FBS <140, RBS <200 mg/dL) should be advised to undertake MNT, physical activity and exercise and weight reduction, with an option of starting pharmacologic therapy (metformin).
- If glycemic targets are not reached within 3 months, then pharmacologic treatment will be started.
- Those who have higher blood sugars, or who are symptomatic should be started right away on one or more pharmacologic agents as applicable (see algorithm) since diet and lifestyle changes are unlikely to achieve the target values.

The following patients must ideally be referred to internists or diabetes specialists (endocrinologists or diabetologists): individuals with Type 1 diabetes; patients who have moderate to severe hyperglycemia; who have co-morbid conditions e.g., infections, acute cardiovascular events such as congestive heart failure or acute myocardial infarction; significant hepatic and renal impairment; or women with diabetes who are pregnant

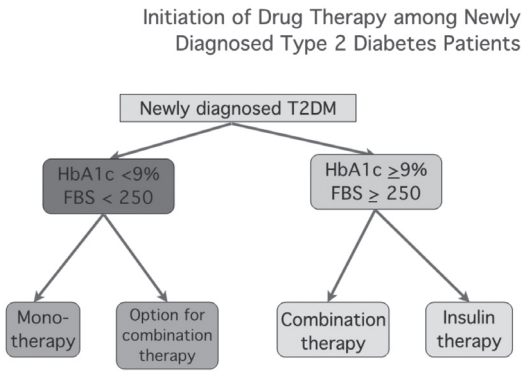

Figure 4. Algorithm for initiation of anti-diabetic agents for newly-diagnosed diabetics.

a. When should combination therapy be considered?

- When glycemic targets are not achieved with one drug given at the maximum effective dose (optimal dose or half maximum), another drug from another pharmacologic class should be added rather than increasing the first drug to its maximum dose.

b. What is the preferred drug?

- Initiate treatment with metformin unless with contraindications or intolerant of its ADE's such as the development of diarrhea, severe nausea or abdominal pain.
- When optimization of therapy is needed, then a second drug can be chosen from the table according to the following considerations: amount of HbA1c lowering, hypoglycemia risk, weight gain, pt profile (dosing complexity, renal and hepatic problems, other contraindications and age). See Table 5.

c. Ideally, all patients who are on insulin or will be started on insulin should be under the care of diabetes specialists (endocrinologists and diabetologists), especially those who are on MDII. These are patients who are inadequately controlled on oral anti-diabetic agents or who have medical conditions which necessitate insulin administration e.g., those needing surgery, presence of infections or pregnant diabetics.

Table 5. Types of Antidiabetic Agents and their Glycemic Efficacy

Drug Class	Action	Examples	Amount of HbA1c lowering
Sulfonyl-ureas (SUs)	Stimulate pancreatic ß-cells to release insulin into the bloodstream	*Chlorpropamide Glipizide Glimepiride Gliclazide Glibenclamide*	1-2%
Meglitinides	Also an insulin secretagogue (but short acting)	*Repaglinide Nateglinide*	0.5-1.5%
Biguanides	Decrease the amount of glucose made by the liver Increases insulin sensitivity of mm & adipose	*Metformin*	1-2%
Thiazolidi-nediones (TZDs)	Improves insulin sensitivity by stimulating PPARγ receptors;	*Rosiglitazone Pioglitazone*	0.5-1.4
Alpha-Glu-cosidase Inhibitors (AGIs)	Block α-glucosi-dase enzymes that break down complex carbo-hydrates into a more absorbable form (simple sugars)	*Acarbose Voglibose*	0.5-0.8%
Dipeptidyl Dipeptidase Inhibitors (DPP4-inhibitors)	Inhibits the action of the DPP4 enzyme which breaks down GLP-1, effectively increasing the levels of GLP-1; causes glucose-dependent increase in insulin secretion	*Sitagliptin Vildagliptin Saxagliptin*	0.5-1.0%

Adapted from JL Jameson. LJ De Groot. Endocrinology: Adult and Pediatric, 6th edition.

Table 6. Safety and Tolerability of Anti-diabetic Agents

Safety Issues	Anticipate this adverse drug reaction for these drugs	Comments
Hypoglycemia	Sulfonylureas, Megletinides, Insulin (esp. human insulins)	Especially true for first generation sulfonylureas and for the second gen SU glibenclamide/ glyburide.
Weight gain	Sulfonylureas, Megletinides, Thiazolidinediones, Insulin	_____
Gastrointestinal symptoms (gastric upset, nausea, loose bowel movements, diarrhea)	Metformin, Alpha-glucosi-dase inhibitors (acarbose), DPP4-inhibitors	For the DPP-4 inhibitors, the expected GI adverse effects are only anorexia, bloatedness, nausea
Lactic Acidosis	Rare ADR from metformin	Avoid metformin among patients already at inherent risk of lactic acidosis e.g., respiratory failure (hypoxemia), severe infections, symptomatic or acute CHF, and those with decreased creatinine clearance. In the US the recommen-dation is to stop metformin at SCr ≥1.5 (1.4 women) and in the UK to decrease the of metformin dose by half for GFR <45 mL/min & stop for GFR <30
Congestive Heart failure, edema	Thiazolidinediones (pioglitazone)	Avoid this drug among those with existing congestive heart failure or those at risk of CHF
Others: Bone Fractures (osteoporosis), Bladder CA	Thiazolidinediones (pioglitazone)	Pioglitazone is contra-indicated among those with a history of bladder cancer; because of the risk for osteoporosis, calcium + vit D supple-mentation might be needed

Table 7. Types of Insulin - Clinical Use and Pharmacokinetics

Type of Insulin	Onset of action	Approximate Peak	Duration of Action	Brand Names
Prandial insulin				
Human regular	0.5-1 hour (inject 30 mins before meals)	2-4 hours	6-8 hours	Humulin R, Actrapid, Generic brands
Rapid acting analogues				
Lispro	10-15 minutes (inject 10-15 mins before meals)	1 hour	3-4 hours	Humalog
Aspart				Novorapid
Glulisine				Apidra
Basal Insulin				
NPH (Human insulin inter-mediate acting)	1-3 hours ,	6-8 hours	12-16 hours	Humulin N, Insulatard, Generic brands
Glargine	1-2 hours Inject anytime, preferably in the morning	Flat (no peak) but maximal effect in 5-6 hours	24 hours	Lantus
Detemir			16-24 hours	Levemir

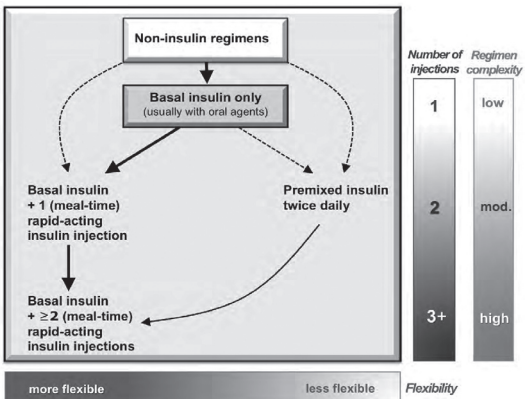

Figure 5. Sequential Insulin Strategies in T2DM

Note: Basal insulin is typically started at a dose of 0.2 units/kg per day (e.g., 50 kg x 0.2 units/kg = 10 units starting dose once a day).

Source: Diabetes Care, Diabetologia. 19 April 2012.

12. Sick Day Management Guidelines

a. How does illness affect glycemic control?

The stress of illness can increase basal insulin requirements in all types of diabetic patients. Being ill may also render the diabetic patient unable to monitor and manage his condition as he would normally.

b. Should the patient adjust/hold his oral antidiabetic medications? If so, when and how?

The patient should take his tablets at the usual dosage provided he can still take in carbohydrates either in solid or liquid form.

If the patient is on a sulfonylurea though, the dose should be reduced if carbohydrate intake is expected to be less.

Glucose monitoring should ideally be done.

If glucose level increases beyond 230mg/dL (13mmol/L), and/or the patient feels unwell, he should see a doctor.

Metformin should be stopped if the patient is becoming dehydrated.

c. For the patient on insulin, should the patient adjust his insulin? If so, when and how?

INSULIN SHOULD NOT BE STOPPED. There are no hard and fast rules regarding insulin dosage as response depends on the individual patient's metabolism and the type of insulin he is taking. Sick-day rules should follow those agreed with consultants/specialist units at the time of initiation of insulin or follow local guidelines.

The following rule of thumb may also be followed:
- Blood glucose less than 13 mmol/L (or less than 230 mg/dL) - continue with current dosage
- Blood glucose 13-22 mmol/L (or 230 to 390 mg/dL) - patient should increase his insulin by 2 units per injection, even if unable to eat
- Blood glucose greater than 22 mmol/L (or 390 mg/dL) - patient should increase his insulin by 4 units per injection, even if unable to eat
- Return dose to normal when blood glucose returns to normal

13. In what situations should the patient see his doctor or go to the hospital right away?

Patients should be advised to seek medical advice if:
- They are unable to eat or drink
- Have persistent vomiting or diarrhea
- Have a blood glucose higher than 25 mmol/L (or 450 mg/dL) despite increasing insulin
- Have very low glucose levels
- Have persistent ketones or large amounts of ketones in the urine
- Become drowsy or confused (make sure carers are aware of this)

Hospital admission should be considered in the following circumstances:
- A suspicion of underlying diagnosis that requires hospital admission, e.g., myocardial infarction, intestinal obstruction
- Inability to swallow or keep fluids down
- Significant ketosis in a type I diabetic despite optimal management and supplementary insulin
- Persistent diarrhea
- Blood glucose persistently >20 mmol/L (or 350 mg/dL) despite best therapy

14. Influenza and Pneumococcal Vaccination for Diabetics

14.1 Will influenza vaccination benefit diabetics? If so, at what age should it be started and how often should it be given?

Recommendations: Influenza (inactivated trivalent) vaccination is recommended for all diabetics >6 months of age, especially those who are >65 years old, residents of chronic care facilities, require regular medical follow-up or hospitalization, or have chronic disorders of the

cardiopulmonary and renal system. (Level 3, Grade B)

Vaccination of health care workers and family of patients with diabetes who can transmit influenza is also recommended. (Level 4, Grade D)

Yearly influenza vaccination is recommended. (Level 4, Grade D)

Summary of the Evidence and rationale:

Influenza is a disease characterized by upper respiratory tract symptoms and fever, which is caused by a constantly mutating virus, resulting in repeated episodes of the illness. It can be caused by any of the 3 influenza virus strains: Type A – moderate to severe illness; Type B – milder illness; Type C – rare. Influenza occurs worldwide. In the Philippines, it occurs year-round, with peaks in July to October.[1] During influenza annual epidemics, rates of morbidity and mortality are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza.[2] One case-control study of people with diabetes showed a 6-fold increased risk of hospitalization during influenza outbreaks compared to nonepidemic years.[3] Cameron et al.[4] reported the odds ratio for death in patients with diabetes as 2.0 (95% CI 0.4–14.8). Independent of diabetes, influenza has been shown to be associated with excess mortality in individuals >65 years of age and in those with cardiovascular and pulmonary diseases.[5,6]

Each year, an inactivated trivalent vaccine is constituted with strains of influenza A and B (2 type A and 1 type B strains). For the Philippines, current recommendations state that the formulation for the Southern Hemisphere be used.[1] In many intervention studies[7-11], it has been demonstrated that vaccination against influenza (during epidemic and nonepidemic years) is associated with less frequent hospitalizations for complications of influenza, fewer deaths during the influenza season, and direct savings in health care costs. Two reviews and a metanalysis support this conclusion[12,13], but none of these reports mentions people with diabetes as a specific population group or as part of an at-risk group. Definitive proof of the efficacy of influenza vaccination specifically in people with diabetes is lacking. There are few randomized controlled trials that have specifically evaluated influenza immunization in people with diabetes because of the large number of patients required and ethical questions of randomization to placebo. Recommendations are based in large part on observational studies.

In the limited studies that included a sufficient number of people with diabetes for statistical power[14], influenza immunization was effective in reducing hospital admissions during influenza epidemics. In a case-control series, influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics.[15] Another nested case-control study demonstrated that influenza vaccination was associated with a 56% reduction in any complication, a 54% reduction in hospitalizations and a 58% reduction in deaths in people with type 2 diabetes.[16] These same studies consistently support influenza vaccination when there are comorbid conditions with diabetes such as age and cardiovascular complications.[17] There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these vaccinations.[18]

Because the vaccine consists of egg-grown viruses, it should not be administered to individuals known to have anaphylactic hypersensitivity to chicken eggs or additional components of the influenza vaccine. Active neurologic disorder, history of developing neurologic symptoms or illness following a previous dose or history of Guillian-Barre Syndrome are also contraindications.[1] Vaccinating individuals at high risk before influenza season each year is the most effective measure for reducing the impact of influenza.[18] Intramuscular dosage and type of influenza vaccine (split or whole virus) vary based on the patient's age.[2] Because infection with influenza virus can be transmitted from person to person, vaccination of health care workers and family of patients with diabetes may be justified.[18]

Because immunity from influenza vaccination declines in the year after vaccination, yearly vaccination is recommended.[18]

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14.2 Will pneumococcal vaccination benefit diabetics? If so, at what age should it be started and how often should it be given?

Recommendations: Pneumococcal vaccination with 23-valent pneumococcal polysaccharide vaccine (PPSV23) or 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for all diabetics >2 years of age, especially those who are >65 years old, residents of chronic care facilities, require regular medical follow-up or hospitalization, or have chronic disorders of the cardiopulmonary and renal system. (Level 3, Grade C)
A one-time pneumococcal revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier. (Level 4, Grade D)

Summary of the evidence/rationale:

Pneumococcal pneumonia is the most common form of acute bacterial community-acquired pneumonia.[1] Bacteremia is seen in 8–50% of individuals with pneumococcal infections, and of these, 15–20% are fatal despite antibiotics.[2] Case fatality rates for children are typically low.[3,4] Adults (50 years of age) have reported fatality rates of 2.4% compared with 1.5% in patients <50 years of age.[5] This high case fatality rate from bacteremic pneumococcal disease supports the concept that a reduction in the number of deaths related to this infection can only be accomplished by widespread immunoprophylactic measures.[6]

Diabetes as well as increased age, an extrapulmonary site of pneumococcal infection, presence of cirrhosis, alcoholism, azotemia, and infection with certain capsular types (such as type 3) appear to contribute the most to risk of death from bacteremic pneumococcal disease.[3,7-11] People with diabetes are susceptible to pneumococcal infection and are at increased risk for the morbidity and mortality of bacteremia from this organism. Additional risk is associated with age >65 years and having chronic cardiovascular, pulmonary, and renal disease.[6]

The current pneumococcal vaccine (23-valent pneumococcal polysaccharide vaccine PPSV23) includes 23 purified capsular polysaccharide antigens representing 85–90% of the serotypes of Streptococcus pneumoniae that cause invasive pneumococcal infections among children and adults.[1]

Cohort and case-control studies have shown vaccine efficacy to be 77–90% for prevention of invasive pneumococcal infection in patients with diabetes.[12-20] There is widespread acceptance that people with diabetes are at least as susceptible to pneumococcal infection as other people with chronic diseases, and therefore the use of the pneumococcal vaccine is encouraged in this population.[6]

As of June 2012, the CDC's Advisory Committee on Immunization Practices (ACIP) expanded the age indication for the 13-valent pneumococcal conjugate vaccine (PCV13) to include adults ages 19 and older who have certain immunocompromising conditions. In randomized, multi-center studies in the United States and Europe, people 50 years and older who received either PCV13 or PPSV23 showed that for the 12 common serotypes, PCV13 induced antibody levels that were either comparable to or higher than the levels induced by PPSV23.The safety of PCV 13 was evaluated in about 6,000 people ages 50 and older.[21,22]

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Summary recommendations on vaccination

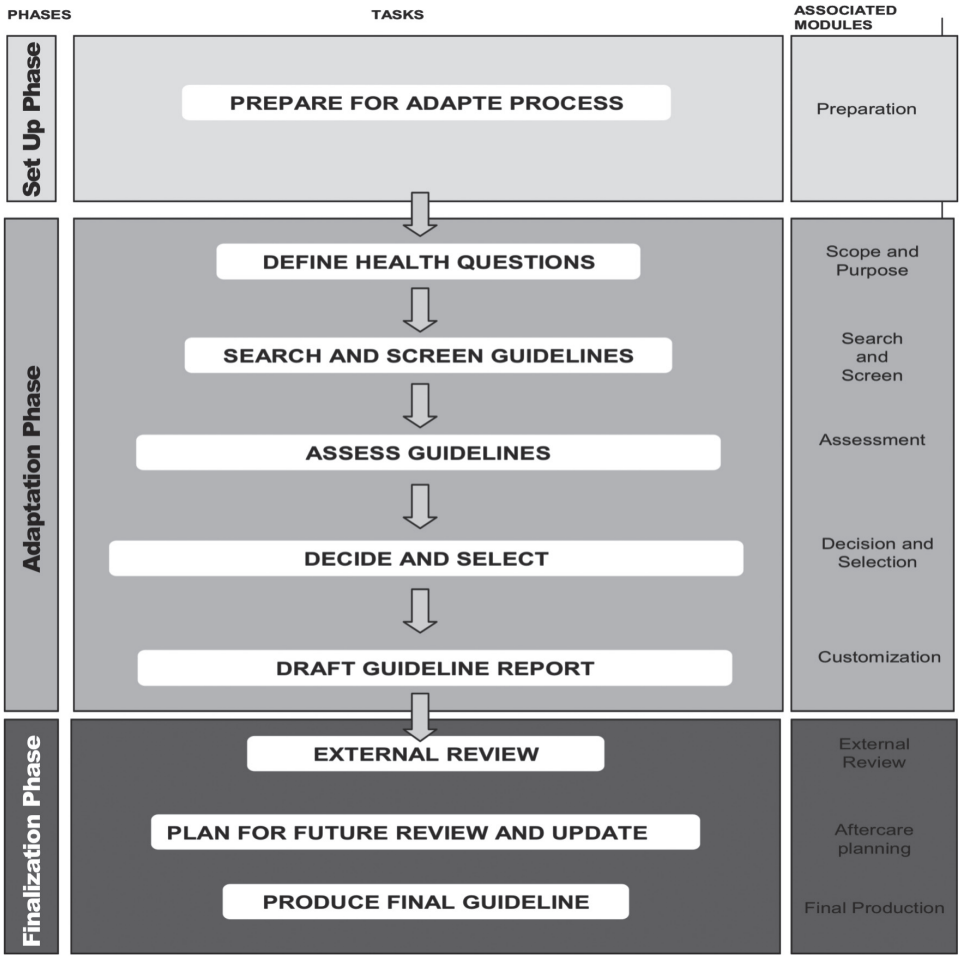
1. Will influenza vaccination benefit diabetics? If so, at what age should it be started and how often should it be given?

- Influenza vaccination is recommended for all diabetics >6 months of age, especially those who are >65 years old, residents of chronic care facilities, require regular medical follow-up or hospitalization, or have chronic disorders of the cardiopulmonary and renal system. (Level 3, Grade B)
- Vaccination of health care workers and family of patients with diabetes who can transmit influenza is also recommended. (Level 4, Grade D)
- Yearly influenza vaccination is recommended. (Level 4, Grade D)

2. Will pneumococcal vaccination benefit diabetics? If so, at what age should it be started and how often should it be given?

- Pneumococcal vaccination is recommended for all diabetics >2 years of age, especially those who are >65 years old, residents of chronic care facilities, require regular medical follow-up or hospitalization, or have chronic disorders of the cardiopulmonary and renal system. (Level 3, Grade C)
- A one-time pneumococcal revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier. (Level 4, Grade D)

APPENDIX A. The ADAPTE PROCESS



APPENDIX B. ADAPTE TOOL 8

Tool 8: Table for Summarizing Guideline Content

		Actual content of guidelines (CPG) (indicate with ☑ if included in guideline)			
		CPG #1	CPG #2	CPG #3	CPG #4
Health question #1					
Health question #2					
Health question #3					
Health question #4					
Health question #5					
Health question #6					
Population	Insert definition here				
Intervention(s)	Insert definition here				
Professionals/	Insert definition here				
Outcome	Insert definition here				
Healthcare setting	Insert definition here				

Appendix C: The AGREE instrument

Tool 9: AGREE Instrument

Available free of charge for download at www.agreetrust.org

The AGREE Instrument - short appraisal form

SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is(are) specifically described.	Strongly Agree	4	3	2	1	Strongly Disagree
2. The clinical question(s) covered by the guideline is(are) specifically described.	Strongly Agree	4	3	2	1	Strongly Disagree
3. The patients to whom the guideline is meant to apply are specifically described.	Strongly Agree	4	3	2	1	Strongly Disagree

STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all the relevant disciplines or stakeholders.	Strongly Agree	4	3	2	1	Strongly Disagree
5. The patients' views and preferences have been sought.	Strongly Agree	4	3	2	1	Strongly Disagree
6. The target users of the guideline are clearly defined.	Strongly Agree	4	3	2	1	Strongly Disagree
7. The guideline has been piloted among target users.	Strongly Agree	4	3	2	1	Strongly Disagree

METHODOLOGY

8. Systematic methods were used to search for evidence.	Strongly Agree	4	3	2	1	Strongly Disagree
9. The criteria for selecting the evidence are clearly described.	Strongly Agree	4	3	2	1	Strongly Disagree
10. The methods used for formulating the recommendations are clearly described.	Strongly Agree	4	3	2	1	Strongly Disagree
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	Strongly Agree	4	3	2	1	Strongly Disagree
12. There is an explicit link between the recommendations and the supporting evidence.	Strongly Agree	4	3	2	1	Strongly Disagree
13. The guideline has been externally reviewed by experts prior to publication.	Strongly Agree	4	3	2	1	Strongly Disagree

14. A procedure for updating the guideline is provided.	Strongly Agree	4	3	2	1	Strongly Disagree

CLARITY AND PRESENTATION

15. The recommendations are specific and unambiguous.	Strongly Agree	4	3	2	1	Strongly Disagree
16. The different options for management of the condition are clearly presented.	Strongly Agree	4	3	2	1	Strongly Disagree
17. Key recommendations are easily identifiable.	Strongly Agree	4	3	2	1	Strongly Disagree
18. The guideline is supported with tools for application.	Strongly Agree	4	3	2	1	Strongly Disagree

APPLICABILITY

19. The potential organisational barriers in applying the guideline have been discussed.	Strongly Agree	4	3	2	1	Strongly Disagree
20. The potential costs implications of applying the recommendations have been considered.	Strongly Agree	4	3	2	1	Strongly Disagree
21. The guideline presents key review criteria for monitoring and/or audit purposes.	Strongly Agree	4	3	2	1	Strongly Disagree

METHODOLOGY

22. The guideline is editorially independent from the funding body.	Strongly Agree	4	3	2	1	Strongly Disagree
23. Conflicts of interest of guideline development members have been recorded.	Strongly Agree	4	3	2	1	Strongly Disagree

OVERALL ASSESSMENT

Would you recommend this guideline for use in practice?

Strongly recommend	
Recommend (with provisos or alterations)	
Would not recommend	
Unsure	

Appendix D. CEBM Levels of Evidence and Strength of Recommendation

Table: Steps in finding evidence ("Levels") for different types of question

Developed by: Iain Chalmers (James Lind Library), *Paul Glasziou* (OCEBM), *Trish Greenhalgh* (UCL), *Carl Heneghan* (OCEBM), *Jeremy Howick (OCEBM), Allesandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton*

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is it? (E.g., Pre-test probabilities)	Most relevant local and current random sample survey (or censuses	Systematic review of current surveys	Systematic review of local non-random sample	Systematic review of case-series	Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms
Is this test accurate? (Diagnostic accuracy)	Systematic review of cross sectional studies	Systematic review of cross sectional studies With consistently applied reference standard and binding	Systematic review of non-consecutive studies, or studies without consistently applied reference standards	Systematic review of case-control study, or cross sectional study with non-independent reference standard	Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms
What will happen if we do nothing? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort or control arm of randomized trial	Systematic review of case-series	Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms
Does this treatment help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational studies with dramatic effect	Non-randomized controlled cohort/ follow-up study	Systematic review of case-control studies, historically controlled studies	Opinion without explicit critical appraisal, based on limited/undocumented experienced, or based on mechanisms
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Systematic review of nested case-control or dramatic effect	Non-randomized controlled cohort/ follow-up study	Case-control studies, historically controlled studies	Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms
What are the RARE harms? (Treatment Harms)	Systematic review of case-control studies, or studies revealing dramatic effects	Randomized trial or (exceptionally) observational study with dramatic effect			
Is early detection wothwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/ follow-up study	Case-control studies, historically controlled studies	Opinion without explicit critical appraisal, based on limited/undocumented experience, or based on mechanisms

*Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

NOTE: Please take note of the asterisk below the table. Following the spirit of the GRADE System, we can downgrade or upgrade the level of evidence given the considerations stated.

Grades of Recommendation
A consistent level 1 studies
B consistent level 2 or 3 studies or extrapolations from level 1 studies
C level 4 studies or extrapolations from level 2 or 3 studies
D level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
(for definitions of terms used see glossary at http://www.cebm.net/?o=1116)
Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.
"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

Appendix E: Procedure for 75-gram Oral Glucose Tolerance Test

Guidelines

The oral glucose tolerance test (OGTT) is recommended by the WHO for diagnosis of T2DM.

Preparation and Cautions

The OGTT should be performed in the morning, after at least three days of unrestricted carbohydrate intake (more than 150 g of carbohydrate daily). The test should not be done during an acute illness, as the results may not reflect the patient's glucose metabolism when healthy. A full test dose of glucose for adults should not be given to a person weighing less than 43 kg, due to the fact that excessive amount of glucose may produce a false positive result.

The OGTT Procedure

The test should be implemented after an **overnight fast of 8 to 14 hours (water is allowed)** following the American Diabetes Association Protocol for the NNHANES. Smoking or physical activity is not permitted during the test. Usually the OGTT is scheduled to begin in the morning (7–9 am) as glucose tolerance exhibits a diurnal rhythm with a significant decrease in the afternoon. At baseline, the blood sample for glucose determination is taken. The patient is then given a glucose solution to drink. The standard dose is 75 g of glucose in 250–300 mL of water. It should be ingested within 5 minutes. For children, the test load should be 1.75 g per kg of body weight, up to a maximum of 75 g of glucose. The next blood sample is collected at 120 min after the glucose load.

Plasma glucose measurement in blood samples

The processing of the samples after collection is important to ensure accurate measurement of plasma glucose. This requires rapid separation of the plasma after collection. Laboratory measurements rely upon the use of separated plasma and only immediate separation can prevent the lowering of the glucose in the sample. Only if the plasma separation is completely impossible to be done immediately upon collection, glycolysis inhibitors, e.g., sodium fluoride (6 mg per mL of the whole blood) can be used. Rapid cooling of the sample may also be helpful in reducing the loss of glucose if the plasma cannot be immediately separated. In this case, the sample should be placed immediately after collection into ice-water but the plasma separation should occur within 30 minutes. The plasma should be frozen until the glucose concentration can be measured.

International Federation of Clinical Chemistry (IFCC) recommended that all glucose measuring devices report the results in plasma values. The reason for this recommendation is the fact that plasma glucose values are approximately 11% higher than the values of whole blood glucose measured in the same sample. Moreover, WHO recommendation is that venous plasma glucose should be the standard method for measuring and reporting. However, it should be noted if one converts from venous to capillary plasma glucose the conversion is different in the case of fasting or post-load glucose values. Fasting values for venous and capillary plasma glucose are identical, while the conversion is necessary only for post-load glucose.

Note: The 75-gm OGTT for pregnant women is similar except that 3 tests are done: FBS, 1-hr and 2-hr post-load blood sugar.

Reference:

Paulweber B et al. IMAGE-Guideline for Diabetes Prevention Horm *Metab Res 2010*; 42 (Suppl. 1): S3–S36