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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(Consensus) Panel of Experts:

<table>
<thead>
<tr>
<th>Associations/Agencies</th>
<th>Representative</th>
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<tbody>
<tr>
<td>Diabetes Philippines</td>
<td>1. Dr. Susan Yu-Gan</td>
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<td></td>
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<td>Associations/Agencies</td>
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<tr>
<td>Diabetes Center (Philippine Center for Diabetes Education Foundation)</td>
<td>4. Dr. Jose Carlos Miranda</td>
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<td>12. Dr. Laura Trajano-Acampado</td>
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<td>13. Dr. Bien J. Matawaran</td>
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<td>Philippine Association of Diabetes Educators (PADE)</td>
<td>14. Dr. Francis Pasaporte</td>
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<td>15. Dr. Ronaldo Toledo</td>
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<td>Philippine Society of Pediatric Metabolism &amp; Endocrinology (PSPME)</td>
<td>16. Dr. Susana Padilla-Campos</td>
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<td>American Association for Clinical Endocrinology (AACE), Phil Chapter</td>
<td>17. Dr. Jose Carlos Miranda</td>
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<td>18. Dr. Yvette Amante</td>
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<td>Association of Municipal Health Officers of the Philippines (AMHOP)</td>
<td>20. Dr. Leonardo Afable Jr.</td>
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<td>Department of Education (DepEd)</td>
<td>21. Dr. Minda U. Meimban</td>
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<td>Department of Health (DOH)</td>
<td>22. Frances Prescilla Cuevas</td>
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<td>(Philippine) Food and Drug Authority (FDA)</td>
<td>23. Dr. Ma. Elizabeth I. Caluag</td>
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<tr>
<td>Association/Agencies Representatives of Diabetic Persons (Lay or Non-medical</td>
<td>24. Charmaine A. Duante</td>
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<td>Representatives)</td>
<td>25. Helena Reginaldo/Marlene Rose Lim</td>
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<td>Nutritionists and Dietitians Association of the Philippines (NDAP)</td>
<td>26. Nieves Serra, RND</td>
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<td>Philippine Academy of Family Physicians (PAFP)</td>
<td>27. Dr. Alex J.B. Alip Jr.</td>
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<tr>
<td>Philippine Association of Medical Technologists (PAMET)</td>
<td>28. Leila M. Florento, RMT, PhD</td>
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<td>Philippine College of Occupational Medicine (PCOM)</td>
<td>29. Dr. Rustico Jimenez</td>
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</table>
Philippine College of Physicians

Philippine Heart Association (PHA)

PhilHealth (NON-VOTING)

Philippine Lipid and Atherosclerosis Society (PLAS)

Philippine Medical Association (PMA)

Philippine Obstetrics and Gynecology Society (POGS)

Philippine Pediatric Society (PPS)

Philippine Society of Hypertension (PSH)

Philippine Society of Nephrology (PSN)

Representative Unable to Attend

30. Dr. Jose Antonio Bautista

31. Dr. Shirley Domingo

32. Dr. Abdias V. Aquino

33. Dr. Arthur Catli

Representative Unable to Attend

34. Dr. Susana Padilla-Campos

35. Dr. Abdias V. Aquino/

Dr. Norbert Lingling Uy

36. Dr. Benjamin Balmores Jr.

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:
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
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
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
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 Endocrinology 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:
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).
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:

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 but 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’s for life. Ideally, they also need to be under the care of diabetes specialists. Type 2 diabetes is usually be 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1 Diabetes Mellitus</th>
<th>Type 2 Diabetes Mellitus</th>
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<tbody>
<tr>
<td>Onset</td>
<td>Acute-symptomatic</td>
<td>Slow-often-asymptomatic</td>
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</table>
| Clinical Picture         | Weight loss, polyuria, polydipsia | If symptomatic, similar picture as T1 DM- weight loss, polyuria, polydipsia
            |                          | • Obese                                                                           |
            |                          | • Strong family history of T2DM                                                          |
            |                          | • Acanthosis NIgricans                                                               |
            |                          | • Polycystic ovary syndrome (PCOS)                                                      |
| Ketosis                  | Almost always present    | Usually absent                                                                         |
| C-Peptide                | Low/absent               | Normal/elevated                                                                        |
| Antibodies               | • ICA positive           | • ICA negative                                                                        |
            | • Anti-GAD positive      | • Anti-GAD negative                                                                    |
            | • ICA 512 positive       | • 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

### SCRENNING 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) (Grade D, Level 5)
- Universal screening using laboratory tests is not recommended as it would identify very few individuals who are at risk. (Grade D, Consensus)
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 \( \geq 40 \) yo
- Consider earlier testing if with at least one other risk factor as follows:
  - History of IGT or IFG
  - History of GDM or delivery of a baby weighing 8 lbs or above
  - Polycystic ovary syndrome (PCOS)
  - Overweight: Body Mass Index (BMI) \( \geq 23 \) kg/m\(^2\) or
    - Obese: BMI \( \geq 25 \) kg/m\(^2\), or
  - Waist circumference \( \geq 80 \) cm (females) and \( \geq 90 \) cm (males), or
    - Waist-hip ratio (WHR) of \( \geq 1 \) for males and \( \geq 0.85 \) for females
  - First degree relative with Type 2 diabetes
  - Sedentary lifestyle
  - Hypertension (BP \( \geq 140/90 \) mm Hg)
  - Diagnosis or history of any vascular diseases including stroke, peripheral arterial occlusive disease, coronary artery disease
  - Acanthosis nigricans
  - Schizophrenia
  - Serum HDL < 35 mg/dL (0.9 mmol/L) and/or
  - 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 2).
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Strength of Association</th>
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<tbody>
<tr>
<td>Previously identified IGT or IFG</td>
<td>both IFG and IGT RR* 12.13 (4.27-20.00)</td>
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<tr>
<td></td>
<td>isolated IGT RR 5.52 (3.13-7.91)</td>
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<tr>
<td></td>
<td>isolated IFG RR 7.54 (4.63-10.45)</td>
</tr>
<tr>
<td>GDM</td>
<td>RR  7.43 (4.79-11.51)</td>
</tr>
<tr>
<td>PCOS</td>
<td>OR for IGT (BMI-matched) 2.54 (1.44, 1.47)</td>
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<tr>
<td></td>
<td>OR for DM2 (BMI-matched) 4.00 (1.97, 8.10)</td>
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<tr>
<td></td>
<td>BMI ≥ 25 kg/m (OR men 1.52 women 1.59)</td>
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<tr>
<td>Overweight or obesity</td>
<td>WC ≥ 90 cm for males and ≥ 80 cm for females (OR men 1.54 women 1.70)</td>
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<tr>
<td></td>
<td>Waist-hip ratio ≥ 1 for males and ≥ 0.85 for females (OR men 1.53 women 1.50)</td>
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<tr>
<td>First-degree relative with DM (parents or siblings)</td>
<td>OR 2.13 (1.22-3.71)</td>
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<tr>
<td></td>
<td>RR for DM based on average hours spent watching TV per week</td>
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<tr>
<td>Sedentary lifestyle</td>
<td>(0-1, 2-10, 11-20, 21-40, &gt;40): RR 1.00, 1.66, 1.64, 2.16, and 2.87</td>
</tr>
<tr>
<td>Conditions assoc with insulin resistance (acanthosis nigricans)</td>
<td>OR 1.97 (1.18-3.27)</td>
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<td></td>
<td>Increased blood pressure, per 1 SD:</td>
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<tr>
<td>HPN</td>
<td>Systolic: RR 1.56 (1.31-1.85)</td>
</tr>
<tr>
<td></td>
<td>Diastolic: RR 1.52 (1.27-1.83)</td>
</tr>
<tr>
<td>CVD</td>
<td>DM as a CVD risk factor (age- and sex-adjusted): HR 2.5 (1.9 to 3.2)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>OR 2.07 (1.03 to 4.15)</td>
</tr>
<tr>
<td>High TG, low HDL or both</td>
<td>Increased triglycerides, per 1 SD: OR 1.70 (1.62-1.78)</td>
</tr>
<tr>
<td></td>
<td>Increased apolipoprotein A-I, per 1 SD: OR 0.76 (0.62–0.92)</td>
</tr>
</tbody>
</table>

* RR= relative risk

**Issue 3.2. In what setting/s should testing for diabetes be done?**
• Testing should ideally be carried out within the health care 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). (Grade B, Level 3)
• Testing at any setting should be supervised by a qualified health care professional. (Grade D, Level 5)

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. (Grade D, Level 5)

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) (Grade D, Level 5)
• 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. (Grade D, Consensus)
• 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 yo.
• Consider earlier testing if with at least one other (other than age) risk factor for diabetes.
• Testing should ideally be carried out within the health care 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). (Grade B, Level 3)
• Testing at any setting should be supervised by a qualified health care professional. (Grade D, Level 5)
References:


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 age10 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
  - Family history (especially parents and grandparents) of Type 2 DM
  - Signs of insulin resistance (Acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small for gestational age birth weight)
  - Maternal history of diabetes or GDM during the child’s gestation

Summary of Recommendations: Screening for Diabetes in children

Screening for pre-diabetes and Type 2 DM is recommended among asymptomatic children commencing at age10 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 $\geq 126$ mg/dL (7.0 mmol/L) after an overnight fast
  - Fasting is defined as no caloric intake for at least 8 hours up to a maximum of 14 hours,
- Two-hour plasma glucose $\geq 200$ 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,
- A random plasma glucose $\geq 200$ 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.\cite{1, 2} It has a sensitivity ranging from 45 to 60% and a specificity of > 90%.\cite{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.\cite{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.\cite{3} Fasting plasma glucose might not detect some patients who are positive with the OGTT.\cite{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. 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. HBA1c was less sensitive for detecting prediabetes or DM compared to OGTT results. 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.

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 ≥ 7.7 to 11.0 mmol/L (140-199 mg/dL) OR 2-hr blood sugar in the 75-gm OGTT ≥ 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. 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.

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. 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. 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). 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.

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. 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. We recommend that patients at risk should therefore be tested more frequently, at least annually if initial tests are negative.

REFERENCES:

Evidences:


4 Dans A, Paz-Pacheco E, Morales D, Sy R et al National Nutrition and Health Survey 2008- oral presentation in the 2010 Annual Convention of the Philippine College of Physicians- Pasay City, Philippines


14 The DECODE Study Group, on behalf of the European Diabetes Epidemiology Group Glucose Tolerance and Cardiovascular Mortality Comparison of Fasting and 2-Hour Diagnostic Criteria, Arch Intern Med. 2001;161:397-404


16 Cosson E, NguyenMT, Ba H, Hamo-Tchantchoue E, Valensi P. Screening overweighted or obese subjects for prediabetes and diabetes: performing directly oral glucose tolerance test in selected patients may be beneficial and cost-effective. In: 5thWorld Congress on Prevention of Diabetes and its Complications. Helsinki:WCPD; 2008


22 Yiling J. Cheng, MD, PHD Edward W. Gregg, PHD1, Linda S. Geiss, MA1, GiuseppeImparatore, MD, PHD1, Desmond E. Williams, MD, PHD1, Xinzi Zhang, MD, PHD1, Ann L. Albright, PHD, RD, Catherine C. Cowie, PH, Ronald Klein, MD, MPH 3and Jinan B. Saadine, MD Association of A1C and Fasting Plasma Glucose Levels With Diabetic Retinopathy Prevalence in the U.S. Population Implications for diabetes diagnostic thresholds Diabetes Care. 2009 Nov;32(11):2027-32.
23 Best practice guidelines for vascular risk assessment and management issued by the UK National Health Service (www.dh.gov.uk/publications)


27 (US adults aged 40 to 79) NHANES III 2005-2006 (K. Flegal, National Center for Health Statistics, personal communication with ADA Task Force on Diagnosis of DM)


42 John D. Sorkin, MD, PhD, Denis C. Muller, MS, Jerome L. Fleg, MD, Reubin Andres, MD
SCRENNING 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. 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]). Hence, universal screening should apply in our population. The DIPS guideline also recommends universal screening for Indian women, because of the high prevalence of gestational diabetes in their population.

The National GDM Technical Working Party of New Zealand recommends that all pregnant women be offered screening for GDM. The NICE guideline recommendation

2 Litonjua AD et al. AFES Study Group on Diabetes in Pregnancy. PJIM 1996; 34:67-68
is similar to that of the ADA where testing is offered to women with any risk factor for gestational diabetes.

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). 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, 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.

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 6.73,66.67]). 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). 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). Once identified, women

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10 Isip Tan IT & Solimen D. Abnormal glucose tolerance and metabolic syndrome in Filipino women with previous gestational diabetes. Unpublished.

with GDM benefit from intensive lifestyle and metformin therapy which reduce the incidence of diabetes by approximately 50%\textsuperscript{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\textsuperscript{1}. The NZGG also recommends risk stratification where “women at high risk of undiagnosed type 2 diabetes should be screened at booking.\textsuperscript{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.\textsuperscript{6}”

Table 3 shows risk factors for diabetes among pregnant women. The odds ratios and positive predictive values from the literature are provided. Note that the ADA\textsuperscript{1} defines macrosomia as birth weight more than 4000 grams while the ASGODIP sets the cutoff at 8 pounds\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR  [95%CI]</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior history of GDM</td>
<td>23.6 [95%CI 11.6, 48.0]\textsuperscript{14}</td>
<td></td>
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<tr>
<td>Glucosuria</td>
<td>9.04 [95%CI 2.6, 63.7]\textsuperscript{15}</td>
<td>50%\textsuperscript{16}</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>7.1 [95%CI 5.6, 8.9]\textsuperscript{17}</td>
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<tr>
<td></td>
<td>2.74 [95%CI 1.47, 5.11]\textsuperscript{14}</td>
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</tr>
</tbody>
</table>


\textsuperscript{13} Litonjua AD et al. AFES Study Group on Diabetes in Pregnancy. PJIM 1996; 34:37-42.

\textsuperscript{14} Ostlund I, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. Acta Obstetricia et Gynecologica Scandinavica 2003;82(2): 103–8


First-degree relative with type 2 diabetes PPV 6.7\%\textsuperscript{16}
First-degree relative with type 1 diabetes PPV 15\%\textsuperscript{16}

Prior macrosomic baby \hspace{1cm} OR 5.59 [95\%CI 2.68, 11.7]\textsuperscript{14}

Age \geq 25 years old \hspace{1cm} OR 1.9 [95\%CI 1.3, 2.7]\textsuperscript{17};
\hspace{1cm} OR 3.37 [95\%CI 1.45, 7.85]\textsuperscript{14}

Diagnosis of polycystic ovary syndrome \hspace{1cm} OR 2.89 [95\%CI 1.68, 4.98]\textsuperscript{18}

Overweight/obese before pregnancy
- BMI \geq 27 kg/m\textsuperscript{2} \hspace{1cm} OR 2.3 [95\%CI 1.6, 3.3]\textsuperscript{17}
- BMI \geq 30 kg/m\textsuperscript{2} \hspace{1cm} OR 2.65 [95\%CI 1.36, 5.14]\textsuperscript{14}

Macrosomia in current pregnancy \hspace{1cm} PPV 40\%\textsuperscript{16}

Polyhydramnios in current pregnancy \hspace{1cm} PPV 40\%\textsuperscript{16}

Intake of drugs affecting carbohydrate metabolism

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**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\textsuperscript{1}. The NICE guideline considers women with previous history of GDM as high risk\textsuperscript{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.”\textsuperscript{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\textsuperscript{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\textsuperscript{20}.

\textbf{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).}

\textbf{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\textsuperscript{19}. However, the ACHOIS provides evidence that treatment of GDM after the 24th week of gestation does reduce complications\textsuperscript{7}. The ADA recommends screening “greater than low-risk women” for gestational diabetes at 24 to 28 weeks gestation\textsuperscript{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\textsuperscript{6}.

\textbf{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).}

\textbf{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\textsuperscript{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\textsuperscript{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\textsuperscript{23}.

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\textsuperscript{22} Sy RAG et al. Viewpoints on Gestational Diabetes: Report from ASGODIP Participating Hospital: Cardinal Santos Medical Center. PJIM 1996;34:45-48
\end{flushright}

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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\textsuperscript{5} and DIPS\textsuperscript{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.\textsuperscript{1} The ASGODIP recommends a GCT for low-risk women at the first prenatal visit and a 75-g OGTT for high-risk women.\textsuperscript{13} The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel\textsuperscript{24} recommends either a fasting plasma glucose, HbA1c or random plasma glucose at the initial visit. If test results are not diagnostic, the panel recommends doing a 75-g OGTT at 24 to 28 weeks of gestation.

The NICE\textsuperscript{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\textsuperscript{26}, more likely to be positive if conducted in the afternoon\textsuperscript{27}, and the results are significantly affected by the time since the last meal.\textsuperscript{28}

A one-step approach using the OGTT is recommended as 10%-\textsuperscript{5} to 23%-\textsuperscript{29} of women fail to return for an OGTT after an initial GCT. Locally, in a study\textsuperscript{30} which used a two-step approach to screen for GDM, 36% of the women failed to return for the diagnostic

\textsuperscript{24} International Association of Diabetes and Pregnancy Study Groups Consensus Panel. IADPSG Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care 2010; 33(3):676-82

\textsuperscript{25} National Collaborating Center for Women’s and Children’s Health. Antenatal care: routine care for the healthy pregnant woman. Commissioned by the National Institute for Health & Clinical Excellence, Mar 2008


\textsuperscript{27} McElduff A & Hitchman R. Screening for gestational diabetes: the time of day is important. MJA 2002; 176(3):136


\textsuperscript{30} Isip-Tan IT, Celzo F. & Abrahan MA. Comparison of the 75-g vs 100-g OGTT in diagnosing gestational diabetes in Filipino women. Unpublished.
OGTT after a positive GCT result. In the ASGODIP data, two hospitals reported that 17.8%\textsuperscript{31} and 48%\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{24} have the advantage of having been based on an analysis of the HAPO study\textsuperscript{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 4. Interpreting the 75-g OGTT Results

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\textsuperscript{31} De Asis TP et al. Incidence of gestational diabetes mellitus at Veterans Memorial Medical Center PJIM 1996; 34:63-66

\textsuperscript{32} Chua-Ho C et al. Screening for gestational diabetes mellitus: Report from ASGODIP Participating Hospital FEU-NRMFH PJIM 1996; 34:43-44


<table>
<thead>
<tr>
<th>75-g OGTT</th>
<th>Threshold(s) for diagnosing gestational diabetes (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IADPSG*</td>
</tr>
<tr>
<td>FBS</td>
<td>92</td>
</tr>
<tr>
<td>1-hour</td>
<td>180</td>
</tr>
<tr>
<td>2-hour</td>
<td>153</td>
</tr>
<tr>
<td>3-hour</td>
<td>NA</td>
</tr>
</tbody>
</table>

a. Any one value meeting threshold is considered gestational diabetes.

b. * Two values must meet thresholds to be considered gestational diabetes.

**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: Capillary Blood Glucose, FBS, RBS, HbA1c, Fructosamine, Urine Glucose

However, if patients already have FBS or RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals. 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.

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%. 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.

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.

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%.

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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


48 Huter O, Heinz D, Brezinka C, Soeller E, Koelle D, Patsch JR. Low sensitivity of serum fructosamine as a screening parameter for gestational diabetes mellitus. Gynecol Obstet


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 the 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 , Level ). 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 2—Metabolic assessments recommended after GDM

<table>
<thead>
<tr>
<th>Time</th>
<th>Test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-delivery (1–3 days)</td>
<td>Fasting or random plasma glucose</td>
<td>Detect persistent, overt diabetes</td>
</tr>
<tr>
<td>Early postpartum (around the time of postpartum visit)</td>
<td>75-g 2-h OGTT</td>
<td>Postpartum classification of glucose metabolism*</td>
</tr>
<tr>
<td>1 year postpartum</td>
<td>75-g 2 h OGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Annually</td>
<td>Fasting plasma glucose</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Tri-annually</td>
<td>75-g 2 h OGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Prepregnancy</td>
<td>75-g 2 h OGTT</td>
<td>Classify glucose metabolism</td>
</tr>
</tbody>
</table>

*Classification of glucose metabolism by criteria recommended by the American Diabetes Association (8). OGTT, oral glucose tolerance test.

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.

**Reference:**

REFERENCES

Clinical Practice Guidelines that were Included in the UNITE for DM CPG: (General Guidelines)

1. American Association of Clinical Endocrinology 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)


7. National Collaborating Centre for Chronic Conditions 2008 (NCCCC)

Clinical Practice Guidelines Included for Gestational DM

1. American College of Obstetricians and Gynecologists (ACOG)

2. American Diabetes Association (ADA)

3. Australasian Guideline

4. International Diabetes Center

5. New Zealand Guidelines

6. NICE Antenatal and NICE GDM Guidelines

7. US Preventive Services Task Force
APPENDIX A. The ADAPTE PROCESS
## Appendix B. ADAPTE TOOL 8

Tool 8: Table for Summarizing Guideline Content

<table>
<thead>
<tr>
<th>Health question #1</th>
<th>Actual content of guidelines (CPG) (indicate with ☑ if included in guideline)</th>
<th>CPG #1</th>
<th>CPG #2</th>
<th>CPG #3</th>
<th>CPG #4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Health question #2</td>
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<td>Health question #3</td>
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<td>Health question #4</td>
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<td>Health question #5</td>
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<tr>
<td>Health question #6</td>
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</tbody>
</table>

Population: Insert definition here

Intervention(s): Insert definition here

Professionals/patients: Insert definition here

Outcome: Insert definition here

Healthcare setting: Insert definition here
### Appendix C: The AGREE instrument

#### Appendix D. CEBM Levels of Evidence and Strength of Recommendation

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

* 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)
(see definitions of terms used see glossary at http://www.cebm.net/?o=1116)

"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 (6mg 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