Alternative tests versus measurement of fasting plasma glucose and oral glucose tolerance test for diagnosis of pediatric type 2 pre-diabetes: a systematic review protocol

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Review question/objective: The gold standard for the diagnosis of pre-diabetes is the measurement of fasting plasma glucose and the oral glucose tolerance test. The objective of this systematic review is to identify all alternative tests currently in use for the diagnosis of type 2 pre-diabetes mellitus in children and establish their accuracy relative to this gold standard.

Keywords Alternative tests; fasting plasma glucose; oral glucose tolerance test; diagnosis of pre-diabetes in children; type 2 pre-diabetes in children


Background

Type 2 diabetes mellitus, which is caused by insulin resistance,¹ was in the past inaccurately named and known as non-insulin-dependent or adult-onset diabetes.² Almost 90% of people with diabetes suffer from type 2 diabetes.² The main cause for its development has been considered to be excess body weight and physical inactivity.³ When type 2 diabetes initially occurs, there may be no symptoms, as such it is usually diagnosed several years after onset when complications have already occurred.

In 2014, 420 million people worldwide had diabetes.⁴ In 2012, diabetes caused 1.5 million deaths and higher-than-optimal blood glucose caused an additional 2.2 million deaths.² In the past, type 2 diabetes mellitus was thought to be a metabolic disorder that only occurred in adults. However, its incidence among children has been rising in the past two decades, so much so that it is currently the main type of children’s diabetes in some parts of the world.⁵-⁷ Although the focus is often on the United States of America (USA), childhood onset type 2 diabetes mellitus occurs in children of all races and in all parts of the world.⁵,⁶

Type 2 pre-diabetes mellitus in children (T2P-DMC) is not as common in Europe as it is in the USA¹⁰; however, its prevalence is rising.² This trend is supported by a recent study conducted in Italy in 2011, which suggests there is a 12.4% prevalence of glucose metabolism alterations among overweight/obese children or adolescents,⁵ whereas in 2002, the prevalence of T2P-DMC and impaired glucose tolerance (IGT) in Italian children was only 0.5% and 5%.¹¹ This research suggests that it is probable that future generations will suffer from more chronic diabetic complications, such as cardiovascular disease, retinopathy, neuropathy and nephropathy and malignant neoplasms, as a consequence. The earlier age of onset also makes it likely that complications will concomitantly occur in younger patients. As such, T2P-DMC is an emerging public health problem.²

Tests and methods for the diagnosis of T2P-DMC are not applied in a standardized fashion between different countries or even within them. There are diagnostic tests for adults’ type 2 pre-diabetes

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metabolic syndrome (MS), which was recognized risk factor for developing type 2 diabetes mellitus.\textsuperscript{1,7,12,13} Metabolic syndrome (MS), which was also once considered to occur only in adults, is now a recognized risk factor for developing T2-Diabetes mellitus.\textsuperscript{14} However, due to ontogenetic development and the differences in metabolic rate in children, it is difficult to establish criteria for identifying MS or type 2 pre-diabetes mellitus in this population.

When considering whether a patient suffers from MS, a minimum of three of five major criteria must be present; in adults, these are defined as: obesity (waist circumference $\geq 102$ cm [40 in] in males and $\geq 88$ cm [35 in] in females), hypertension (blood pressure $\geq 130/85$ mmHg), fasting glucose $>110$ mg/dL, triglycerides $\geq 150$ mg/dL and high density lipoproteins-cholesterol $< 40$ mg/dL.\textsuperscript{15} The International Diabetes Federation (IDF) provides measurement values for the investigation of MS in children. Many of the criteria used to define the presence of MS, and MS itself, are risk factors for the development of type 2 pre-diabetes mellitus.\textsuperscript{16} These values will be used to determine whether children are at risk of T2P-DMC in the inclusion criteria.\textsuperscript{14,15}

The screening of at-risk children at the different ontogenetic stages (six to 10, 10–16 and $>16$ years) has been recommended to be carried out every two years or at the onset of puberty by the ADA.\textsuperscript{1} The gold standard for the diagnosis of pre-diabetes is the fasting plasma glucose (FPG) test carried out along with the oral glucose tolerance test (OGTT). Early diagnosis of T2P-DMC is crucial for early therapy, and the prevention of complications of diabetes that seriously affect public health all around the world. However, fasting (as required by the FPG test) can be difficult to implement in children, and the OGTT requires a two-hour period of waiting between the administration of glucose and the assessment of glucose tolerance. Both of these factors have been noted as impediments to the routine screening and diagnosis of T2P-DMC.\textsuperscript{17,18} As such, there is a move toward the development of tests which can be more conveniently applied in children.\textsuperscript{17-19}

It is projected that by 2030 diabetic complications will be a leading cause of death in developed countries.\textsuperscript{20} However, there are no guidelines for clinical practice or systematic reviews for child populations that investigate alternate tests for the investigation and diagnosis of T2P-DMC. We searched the JBI Database of Systematic Review and Implementation Reports, PROSPERO database and Cochrane Library in February 2016, and found no developed systematic review or protocols on this topic. The need for a practical, accurate diagnostic test for pediatric patients is great due to the epidemic of childhood obesity in developed countries. As such, this systematic review of diagnostic test accuracy\textsuperscript{21,22} is being conducted to synthesize the best available evidence on the diagnostic test accuracy of alternative tests (that can be carried out more readily in children) compared to the gold standard ADA tests (glucose tolerance test, FPG). An additional aim of this systematic review is to identify which alternative tests are currently being utilized for the diagnosis of T2P-DMC as to date there has been no systematic attempt to identify and describe available alternatives to the FPG test and OGTT.

**Inclusion criteria**

**Types of participants**

The current review will consider studies which include children up to 18 years of age at risk of developing T2P-DMC. At-risk children will be defined as those with any of the following characteristics: obesity, hypertension, low HDL levels, elevated triglyceride levels and glucose intolerance. The IDF\textsuperscript{14,15} has set criteria for how the above conditions should be defined for different stages of ontogenetic development (six to 10, 10–16, and $>16$ years) which will be applied. Studies with participants over 18 years will be excluded.

**Index test**

The current review will consider studies that evaluate alternate (not currently recommended by the ADA) diagnostic or screening tests for pre-diabetes as index tests. These will include but not be limited to any non-fasting tests, homeostatic model assessment of insulin resistance (a mathematical index that uses fasting glucose and insulin to measure insulin resistance), measurements of serum glucose and insulin, HbA1c and 1,5 anhydroglucitol.
Reference test

The reference test will be the tests considered to make up the gold standard for the diagnosis of pre-diabetes by the ADA for the diagnosis of pre-diabetes. These are the measurement of FPG and the OGTT. Normal fasting glucose is defined as fasting glucose \( \leq 99 \text{ mg/dL} \), whereas fasting glucose between 100 and 125 mg/dL indicates IFG and pre-diabetes (higher values suggest diabetes). Normal glucose tolerance is defined as glucose \( \leq 139 \text{ mg/dL} \) 2 h after glucose intake, whereas IGT is defined as a 2-h glucose level of 140–199 mg/dL.

Diagnosis of interest

The current review will consider studies that have the diagnosis of type 2 pre-diabetes mellitus as their diagnosis of interest.

Types of studies

The current review will consider diagnostic cross-sectional study designs for inclusion. Diagnostic case-control studies will also be included; however, as they are at risk of overestimating the accuracy of tests, they will only be incorporated in meta-analysis if there is a lack of cross-sectional studies.

Search strategy

The search strategy will use mainly subject headings and text words related to the issue which are tailored for each included database. The search strategy aims to find both published and unpublished studies. A three-step search strategy will be used in this review. An initial search will be done in two databases: Ovid MEDLINE and Embase where terms such as “children”, “HOMA”, “HbA1c”, “oral glucose tolerance test”, “pre-diabetes mellitus type two” and “metabolic syndrome” will be used. This initial search will be followed by an analysis of the text words contained in the titles and abstracts. In addition, index terms describing articles will be assessed. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified papers and reports and articles will be searched for additional studies. Studies published in all possible languages (if their titles and abstracts are available in English) will be considered for inclusion in the systematic review. In those studies in which their titles and abstracts are approved to be eligible for inclusion, the complete manuscript will be translated. For this review, no time restriction will be considered.

The databases to be searched include: MedLine@ Ovid MEDLINE, Biomedica Czechoslovakia, Embase, CINAHL, Web of Science and Scopus. The search for unpublished studies will include: Open Grey, Current Controlled Trials, MedNar, ClinicalTrials.gov, Cos Conference Papers Index, International Clinical Trials Registry Platform of the World Health Organization and Google Scholar.

The initial key words to be used in the first search are presented in Appendix I.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers (DT and TL) for methodological validity prior to inclusion in the review using the JBI diagnostic test accuracy review instrument Critical appraisal checklist which is based on quality assessment of diagnostic accuracy studies. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (MK). All studies, regardless of their methodological quality, will be included in the review. Analysis of sensitivity will be performed to assess if the results are influenced by methodological quality.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction instrument from the diagnostic test accuracy chapter in the JBI Reviewers’ Manual. The data extracted will include specific details about the populations, index tests and diagnosis of interest relevant to the review question and objectives. If there are data missing or incomplete, the reviewers will contact the authors of the primary studies. Two reviewers (DT and JL) will extract data independently. If there is disagreement, a third reviewer (MK) will be involved.

Data synthesis

Diagnostic data, where possible, will be pooled in statistical meta-analysis. Data will be presented graphically in two ways. Forest plots will be used for sensitivity and specificity for each of the selected primary studies. This graph will display the means and confidence intervals for sensitivity/specificity. These values will be also expressed in numerical form. Moreover, the number of true positives, false
positives, true negatives and false negatives will be also reported. If possible, summary receiver operating characteristic curves will be created. The Bivariate model for meta-analysis will be used. Initially, clinical heterogeneity will be assessed by determining whether the studies are sufficiently similar to pool in terms of the inclusion criteria. If they are clinically homogeneous, statistical heterogeneity will be assessed using the standard Chi² test (significance level: 0.1). If heterogeneity is found, it will be carefully investigated by comparing the characteristics of the differing studies. If this comparison suggests that the heterogeneity is due to the existence of specific risks of bias in some studies, then meta-analysis will be restricted to studies which do not possess the identified risks. Sub-group analysis is planned based on type of study design if possible (case-control compared to cross-sectional).

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References
## Appendix I: Initial search keywords

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<thead>
<tr>
<th>P</th>
<th>1. Children OR teenager OR kid OR non adults OR early ontogenetic stage OR youngster OR adolescent OR youth OR child OR young OR youth diabetes OR juvenile diabetes</th>
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<tr>
<td>I</td>
<td>2. HOMA OR HOMA-IR OR homeostatic model assessment of insulin resistance OR postprandial glucose test</td>
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<td>3. HbA1c OR H$\text{smoglobin}$ A1c OR OR glyco$h\text{smoglobin}$ OR h$\text{smoglobin}$ A1c OR A1c OR A1c h$\text{smoglobin}$ OR HGBA1C OR hemoglobin A1C</td>
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<td>4. 1.5 anhydroglucitol OR 1.5 – AG OR anhydro-d-glucitol OR glycoMark OR anhydroglucitol OR dianhydro-d-glucitol</td>
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<td>R</td>
<td>5. OGTT OR oral glucose tolerance test</td>
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<td>6. FPG OR fasting plasma glucose</td>
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<td>D</td>
<td>7. Type 2 pre-diabetes mellitus OR insulin resistance OR impaired glucose tolerance OR impaired glucose metabolism OR type 2 diabetes OR non-insulin dependent diabetes</td>
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<td></td>
<td>8. Diag$^*$ OR sensitivity OR specificity OR predictive value OR ROC OR receiver operating characteristic</td>
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