Title: Fructosamine measurement for diabetes mellitus diagnosis and monitoring: A systematic review protocol

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Abstract

Introduction: Tight metabolic control is the basis of contemporary diabetes mellitus (DM) management. Fructosamine is a marker of glucose control reflecting the average glycemic level over the preceding 2-3 weeks. Its measurement is quick, technically simple, inexpensive, precise, fairly free of interferences, unaffected by red blood diseases and easily automated for use with micro-sample volumes. However, fructosamine has not gained as much popularity as glycated hemoglobin (HbA1c) for DM control monitoring, and the related underlying reasons remain unclear. We aim to search for and summarize currently available evidence on the accuracy of fructosamine measurements to diagnose and monitor DM. We are not aware of previous systematic reviews that have looked at this issue.

Methods and analysis: This is a systematic review of the literature. We will include randomized control trials (RCTs), controlled before-and-after studies, time series designs, cohort studies, case–control studies and cross-sectional surveys reporting the diagnosis and/or monitoring of DM (type 1 DM, type 2 DM, and gestational diabetes) with fructosamine compared to other measures of glycemia (fasting glucose, oral glucose tolerance test, random glucose, HbA1c), without any language restriction. We will perform electronic searches in PubMed, Scopus and other databases, supplemented with manual searches. Articles published from the 1st January 1980 to present will be eligible for inclusion in this review.

Two authors will independently screen, select studies, extract data and assess the risk of bias with discrepancies resolved by consensus. We will assess clinical heterogeneity by examining the types of interventions and outcomes in each study and pool studies judged to be clinically homogenous. We will also assess statistical heterogeneity using the chi-square test of homogeneity and quantify it using the I-square statistic. Absolute accuracy measures (sensitivity, specificity) will be pooled in a bivariate random effects model, allowing for inter-
setting variability. Negative and positive predictive values will be computed for fructosamine compared with another measure of glycemia from the pooled estimates of sensitivity and specificity using Bayes’ theorem.

*Ethics and dissemination:* This systematic review will use data from published studies and does not require ethics approval. Findings will be published in a peer-reviewed journal and presented at relevant scientific conferences.

*Protocol registration number:* This protocol has been designed according to the PRISMA-P 2015 guidelines, and registered with PROSPERO (ID = CRD…*)
Introduction

Rationale

Diabetes mellitus (DM), particularly type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide, fuelled by population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. Estimates from International Diabetes Federation (IDF) indicate that the number of adults with DM in the world will expand by 55%, from 381.8 million in 2013 to 591.9 million in 2035 (1). DM causes significant morbidity, disability and premature mortality through micro- and macro-vascular complications such as cerebrovascular disease, retinopathy, coronary heart disease, peripheral artery disease, nephropathy, and neuropathy (1). Nevertheless, there is body of evidence demonstrating that the onset and progression of DM complications can be prevented or delayed by achieving and maintaining near-normal metabolic control of the disease (2-4). Accordingly, tight metabolic control is the basis of contemporary diabetes management. For this purpose, simple, reliable, affordable and easily reproducible tests are needed to monitor the outcomes of diabetes care and provide timely feedback to the management.

Glucose monitoring in diabetes focuses on both acute and long term changes. Acute term diabetes control monitoring has been traditionally based on fasting or post-prandial blood glucose measurements, and provides useful information for daily adjustment of management strategies. Unfortunately, blood glucose concentrations fluctuate substantially and a single spot sample is insufficient to accurately characterize glycemic control status, and implementing multiple blood glucose testing appears to be cumbersome to patients. Long term diabetes control builds on parameters of chronic hyperglycemia existing in the forms of glucose non-enzymatically bound to naturally occurring proteins (5), and that are less
sensitive to daily fluctuation in blood glucose levels, thus obviating the need for too frequent
testing.

Fructosamine, discovered about 30 years ago, is a marker of glucose control reflecting the
average glycemic level over the preceding 2-3 weeks (6). Consequently, it may be more
appropriate for monitoring early response to treatments (6). Fructosamine measurement is
quick, technically simple, inexpensive, precise, fairly free of interferences, unaffected by red
blood diseases and easily automated for use with micro-sample volumes (7-10). Therefore,
fructosamine has been proposed as a suitable parameter to monitor glycemic control
throughout pregnancy(11, 12), in low-income countries (13) and in areas where high
prevalences of sickle cell disease and sickle cell traits have been reported (14, 15). However,
fructosamine has not gained as much popularity as glycated hemoglobin (HbA1c) for DM
control monitoring, despite some reports claiming that fructosamine could outperform HbA1c
(16, 17).

The current protocol is for a systematic review to assess the accuracy of fructosamine
measurements to diagnose and monitor the management of type 1 DM (T1DM), type 2 DM
(T2DM) and gestational DM (GDM). We are particularly interested in answering the
following questions: (i) what is the performance of fructosamine measurement in diagnosing
diabetes vs. traditional measurements (fasting glucose, oral glucose tolerance test (OGTT),
random glucose, HbA1c), (ii) are baseline fructosamine levels associated with future
occurrence of diabetes complications, and (iii) how does fructosamine compared with other
measures of glycaemia (OGTT, fasting glucose, HbA1c, random glucose) predict future
occurrence of diabetes complications?

Objective
To conduct a systemic review and meta-analysis of studies published from 1980 to date in order to assess the accuracy of fructosamine measurement for diagnosing DM (T1DM, T2DM and GDM), and monitoring the management of the disease.

Methods and analysis

Eligibility criteria

Inclusion criteria

- We will include randomized control trials (RCTs), controlled before-and-after studies, time series designs, cohort studies (either prospective or retrospective), case–control studies and cross-sectional surveys.
- The cross-sectional survey must have investigated the performance of fructosamine measurement in diagnosing DM (T1DM or T2DM or GDM) vs. traditional measurements (fasting glucose, OGTT, random glucose, HbA$_{1c}$).
- The follow-up studies must have reported either the baseline fructosamine levels that are associated with future occurrence of diabetes complications, or fructosamine capacity to predict future occurrence of diabetic complications when compared with other measures of glycemia.
- We will consider all published and unpublished studies reported from 1st January 1980 to present in human subjects neither with any sex nor origin (country) restriction, and account for the change in diagnosis and control criteria for diabetes mellitus over time. No language restriction will be applied.

Exclusion criteria

The following studies will not be considered in the present review:

- Studies not performed in human subjects
- Studies reported before 1st January 1980
- Letters, reviews, commentaries and editorials
- Studies lacking primary data and/or explicit method description
- Duplicates; for studies published in more than one report, the most comprehensive and up-to-date version will be used.

**Information sources**

**Electronic databases**

We will perform electronic searches in PubMed MEDLINE, EMBASE, Google Scholar, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science (Science Citation Index), OCLC (Paper First and Proceedings First), PAIS International Database (EBSCO), WHO Global Health Library, and POPLINE. Table 1 displays the PubMed search strategy. This strategy will be adapted as appropriate for other databases. Information on unpublished or ongoing studies will be sought through the WHO International Clinical Trial Registry Platform, Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR), the WHO Global Infobase and the meta-Register of Controlled Trials (mRCT).

**Searching other resources**

Manual searches will include scanning the reference lists of relevant studies, specialist journals and conference proceedings.

**Search strategy**

We will perform a comprehensive search of the peer-reviewed and grey literature to identify all appropriate studies available from 1st January 1980 to the present time, and fulfilling our inclusion criteria. The methods for this systematic review are developed according to the
Study records

Data extraction and management

Two authors will independently extract data from included studies using a standardized data extraction form that will be developed for this review. For each study, we will collect general information (authors, year, country, type of publication), study design and methodology, sample size, age range, the type of assay performed to measure fructosamine, other tests of glycemia, study findings and outcomes. From each study comparing fructosamine to other measures of glycemia (fasting glucose, OGTT, random glucose, HbA1c), we will extract data on sensitivity, specificity, positive and negative predictive values and other measures of predictive accuracy when available, or we will extract the data needed to estimate those performance measures. The two authors will compare the extracted data and resolve discrepancies by discussion and consensus, or arbitration of a third author. Relevant missing data will be sought by contacting the corresponding authors of included studies.

Selection process

We will develop and pilot a study selection guide using the inclusion criteria described above to make sure that the criteria are clear and can be applied consistently by all review authors. Two authors will independently screen the titles and abstracts obtained from the searches and retrieve the full text of records deemed potentially eligible by at least one of the two authors. The two authors will afterwards independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion and consensus. If a decision is not reached, a third review author will be consulted.
Data collection process

Internationally approved methodology for data collection and analysis will be used based on the guidance of the Cochrane Handbook of Systematic Reviews for Interventions (20).

Risk of bias in individual studies

Two reviewers will independently assess risk of bias in each included study using the QUADAS-2 tool for the quality assessment of diagnostic accuracy studies (21). We will provide a thorough description of the missing data and dropouts for each included study, and the extent to which these missing data could have influenced the results of the study. The authors will compare their results and resolve any differences by discussion and consensus. Risk of bias and quality scores will be presented in a table and a flow diagram.

Data synthesis including assessment of heterogeneity

We will pool studies found to be clinically homogeneous through a random-effects meta-analysis. Clinical heterogeneity will be investigated by examining the design and setting, the type of assay used to measure fructosamine, the types of interventions and the outcomes in each study. Statistical heterogeneity will be investigated using the $\chi^2$ test of homogeneity on Cochrane’s Q statistic (22), and we will quantify any between-study heterogeneity using the I$^2$ statistic (23). Absolute accuracy measures (sensitivity, specificity) will be pooled in a bivariate random effects model, allowing for inter-setting variability (24). We will jointly illustrate the absolute pooled sensitivity and specificity for fructosamine using Hierarchical Summary Receiver Operating Characteristic (HSROC) regression curves (25, 26). Negative and positive predictive values will be computed for fructosamine compared with another measures of glycemia from the pooled estimates of sensitivity and specificity using Bayes’ theorem. The pooled relative sensitivities and specificities of fructosamine compared with each of the other measures of glycemia will be obtained from the pooled absolute accuracy
measures assessed by a bivariate model with the method of moments (27), allowing for inter-setting variability. If the included studies differ significantly in design, settings, outcome measures or otherwise, we will summarize the findings in a narrative format.

MADA package of the statistical software R (The R Foundation for statistical computing, Vienna, Austria) will serve for bivariate meta-analysis of sensitivity and specificity (28), and MVMETA package for assessing pooled relative sensitivities and specificities (27). Statistically significant results will be set at a p value < 0.05.

**Meta-biases**

Publication bias will be assessed with funnel plots of the diagnostic odds ratios, complemented with the use of Egger’s test of bias. Additionally, the trim-and-fill method will be applied to assess the impact of potential publication bias (29).

We will present a table of the main characteristics of included studies and a summary table for potentially eligible studies that were subsequently excluded, and reasons for exclusion. Findings will be reported by time period, to account for changes of the criteria for diagnosing and monitoring diabetes over time.

Methods, findings and implications of the findings of this systematic review will be reported according to the PRISMA guidelines, including the extended guidance on reporting equity-focused systematic reviews (18, 19). This protocol has been presented with regard to the PRISMA-P 2015 guidelines (30), and registered with PROSPERO (ID = CRD…).

**Ethics and dissemination**

The systematic review does not require ethical approval since it is based on published studies and not individual participant data. The findings of this systematic review are expected to have important implications for clinical practice and research. The review will shed light on
the potential use of fructosamine to diagnose or monitor T1DM, T2DM, and GDM, especially in resource-poor settings and in situations where HbA1c measurement are imprecise (9, 10, 13). The findings of this systematic review will be published in a peer-reviewed journal and shared at relevant scientific conferences.

**Conflict of interest**

None with this article

**Authors’ contributions**

JRNN, APK and JJNN conceived and designed the protocol, and JRNN drafted the manuscript. APK, JJNN, ES, JFD, and EVB critically revised the manuscript for methodological and clinical content. All authors approved the final version of the manuscript.

**References**


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