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Effects of physical exercises on glycosylated hemoglobin, inflammation and neuropathic index in diabetic conditions

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 July 2023 and was last updated on 08 July 2023.

INTRODUCTION

Review question / Objective Review Question; The review question for this study are: What are the effects of physical exercises on glycosylated hemoglobin in people living with diabetes? What are the effects of physical exercises on inflammation in people living with diabetes? What are the effects of physical exercises on peripheral neuropathy in people living with diabetes? Objective of study: To answer the review question, specific objectives were formulated, namely, to determine the effects of physical exercises on: - 1)glycosylated haemoglobin 2)Inflammation and 3) Neuropathic indices in patients with diabetes mellitus.

Rationale The rationale of this study is to determine the evidence of effects of physical exercises on glycosylated hemoglobin, inflammation and neuropathic index in diabetic conditions and appraisal from the literature that will guide clinical practice.

Condition being studied Diabetes is a chronic metabolic disorder that are characterized by hyperglycemia and occurs as a result of inadequate production of insulin or because of the body cells do not respond appropriately to insulin.
Types of diabetes
1. Insulin dependent diabetes mellitus (IDDM), also known as type 1 diabetes, which usually occurs in childhood and young adulthood. Type 1 diabetes is caused by complete deficiency of insulin secretion due to autoimmune destruction of the insulin-producing b-cells of the islets of Langerhans.\
2. Non Insulin dependent diabetes mellitus (NIDDM), also known as type 2 diabetes, can be associated with resistance to insulin action and the deficiency of insulin secretory response.
3. Gestational diabetes mellitus (GDM), is defined as a glucose intolerance resulting in hyperglycemia that is first recognized during pregnancy.

METHODS

Search strategy An extensive study strategy was developed for the PubMed using search terms

from Medical Subject Heading (MeSH), entry terms and keywords in the titles, abstract and text for the population, intervention, control and outcomes. A pilot search was first conducted to determine the sensitivity and specificity of the search strategy. The search strategy was modified to the syntax and subject heading of the other bibliographic databases. The modification also included the use of Boolean operators and search truncations for the searches. Hand searches were also conducted from the reference list of identified studies and suggested articles as well as a search of the grey literature. A PubMed search is included in Table 3.1. The detail of the strategy is shown in Appendix I and II. Overall, seven databases were searched including: CINAHL, the Cochrane Central, Medline, Pubmed, psycINFO, Web of science and Scopus. Trial registers and directory of open-access repository websites including http://www.clinicaltrial.gov., http://www.opendor.org. and the Web of science conference proceedings, were searched.
Search terms
Concept Search terms
Population MeSH terms: Diabetes milletus
Free text terms: T1D, T2D, Gestational diabetes
Intervention MeSH terms: Exercise
Free text terms: Physical activity, physical exercise, Exertion, supervised exercise, long term exercise, sustained exercise, exercise program, home based exercise, aerobic training, strength training.
Comparator MeSH terms: clinical trials
Free text terms: Clinical trial, placebo, randomly, randomized, trial
Outcomes MeSH terms: Inflammation, glycosylated haemoglobin, neuropathy
Free text terms: CRP, TNF-a, IL-1b, Il-6, HbA1c, polyneuropathy, peripheral neuropathy
In addition to the electronic searches;
published systematic reviews of exercise interventions; reference lists of relevant articles and books; the Cochrane systematic review database; the Database of Abstracts of Reviews of Effects (DARE); the National Institute of Health Research (NIHR) portfolio for recently completed or ongoing studies; and the current controlled trials register and hand searches were conducted to identify relevant RCTs.

Participant or population This review included studies on exercise interventions which involved individuals living with diabetes mellitus (without another disease condition). Studies were included in this review so far that they involved adult human participants (between 18-80 years) that participated in physical exercises irrespective of gender, and disease type, but with a duration of not less than 4 weeks. No specific limitation was considered with regards to the study setting. Additionally, studies were included in this review regardless of whether they were conducted in clinics, health centers, hospitals or community settings.

Intervention Different exercise interventions targeted at patients with either T1D or T2D, were included, especially interventions that were supervised exercise programs. Inclusion was not restricted to a particular form, dose, duration, frequency, and intensity of intervention or follow - up period post-intervention.

Comparator Patients who were placed on medications, insulin, dietary control or weight loss would be used. No limitation was placed as regards the type of drug therapy.

Study designs to be included Only original research manuscripts published in English language in peer-reviewed journals and Conferences proceedings were included in this review. This review included RCTs that evaluated the effects of physical exercise (aerobic, resistance or combined) interventions on glycosylated haemoglobin, inflammation and neuropathy in patients with diabetic conditions.

Eligibility criteria The eligibility criteria considered for selecting studies for the review includes:3.1.1 Inclusion Criteria1 Types of Studies:Only original research manuscripts published in English language in peer-reviewed journals and Conferences proceedings were included in this review. This review included RCTs that evaluated the effects of physical exercise (aerobic, resistance or combined) interventions on glycosylated haemoglobin, inflammation and neuropathy in patients with diabetic conditions.2 Types of participants:This review included studies on exercise interventions which involved individuals living with diabetes mellitus (without another disease condition). Studies were included in this review so far that they involved adult human participants (between 18-80 years) that participated in physical exercises irrespective of gender, and disease type, but with a duration of not less than 4 weeks. No specific limitation was considered with regards to the study setting. Additionally, studies were included in this review regardless of whether they were conducted in clinics, health centers, hospitals or community settings.3 Types of interventionsRCTs of different exercise interventions targeted at patients with either T1D or T2D, were included, especially interventions that were supervised exercise programs. Inclusion was not restricted to a

particular form, dose, duration, frequency, and intensity of intervention or follow - up period post-intervention.4 Types of control: RCTs of patients who were placed on medications, insulin, dietary control or weight loss would be used. No limitation was placed as regards the type of drug therapy.5 Timing:Inclusion of studies was done so long as they specified that an assessment of the outcomes was done immediately on the completion of the intervention and/or at ≤ 6 months post-intervention. 6. Types of outcome measures:Studies were included in this review if they reported on changes in the outcome of interest, specifically: inflammatory cytokines (CRP, TNF-a, IL-6, IL-1b), glycosylated haemoglobin (HbA1c), and neuropathic indices. The primary outcome was the serum level of the glycated haemoglobin (HbAic) while the inflammatory biomarkers ((CRP, TNF-a, IL-6, IL-1b) and neuropathic indices were the secondary outcomes. All studies on any particular type of outcomes were included as far as an unambiguous free analysis was carried out for each outcome. All outcome variables were collated and accounted for in each study. No modification of original description in the individual studies was done, and clinical results were analysed and graded as they appeared in the original studies.2.1.2 Exclusion Criteria• Studies without an exercise or physical activity intervention.• Studies that have an exercise intervention but did not report on the primary outcome measure (i.e., HbAic) for this review. • Studies with an exercise intervention, but was not conducted on the involved population.• Studies with pregnant and adolescent participants. • Studies with participants that are diabetic with the coexistence of another condition (such as obesity)• Narrative review syntheses, systematic reviews, opinion papers, publication and any letter without detailed description of methods and/or primary data.• Studies that are not Randomized controlled trials or RCTs including those that are of exploratory design.• Studies without baseline similarities.• In duplicate publications from the same study, the most recent and topic-related publication was used.

Information sources An extensive search strategy to identify studies that were eligible for inclusion into this review was implemented including the search of bibliographic database, grey literature and eligibility criteria system of study inclusion. This procedure was implemented in accordance with the rules of the Cochrane Handbook of Systematic Reviews of Interventions (Higgins & Green, 2014) and advice for Health Care Review by the Centre for Reviews and Dissemination (Makers 2009).

Main outcome(s) The primary outcome was the serum level of the glycated haemoglobin (HbAic) while the inflammatory biomarkers ((CRP, TNF-a, IL-6, IL-1b) and neuropathic indices were the secondary outcomes.

Data management Export of search results to Refworks manager was done to manage the bibliographic records including checking for and removing duplicates of the identified studies from the databases. Bibliographic records were exported from Refworks manager into Microsoft Excel (Microsoft 2010) to aid the screening of the articles based on the eligibility criteria.

Selection Process

Inclusion criteria were utilized in identifying applicable studies. Initial screening of title and abstract was conducted by two independent reviewers (Reviser 1 - GC and Reviewer 2 - CO) to identify potentially relevant studies. The two reviewers independently screened the full text of the selected studies to identify studies that met the inclusion criteria. Differences in opinion regarding whether any paper should be included in the review occurring at any stage were resolved through discussion and reflection, in consultation with the Reviewer 3 (PSCI) if the need arose. When decision cannot be made with the available information, study authors were contacted (up to the maximum of three email attempts) to clarify issues of selection of any study. Studies were excluded with reasons recorded if authors failed to respond to requests for clarifications on issues that were unclear. Details of study flow through the selection process were presented, along with the reasons for exclusion in a PRISMA flow chart.

Data Collection Processes

Quality Appraisal for Included Studies

The methodological rigour of the selected studies was assessed using the Physiotherapy Evidence Database (PEDro) quality appraisal tool. The PEDro is an 11-item scale in which the first item relates to external validity and the other ten items assessing the internal validity of a clinical trial. One point is assigned for each satisfied criterion (except for the first item) until a maximum score of 10. The higher the score, the better the quality of the study and the point scale is interpreted as follows: 9-10 (excellent); 6-8 (good); 4-5 (fair); <4 (poor). A point for a specific criterion was awarded only if the article gave a detailed report that the criterion was met. A score of one was given for each “yes” answer and zero for “no,” unclear and not applicable (N/A) answers. The overall score was reported as a tally of all “yes” answers out of the 10 maximum points depending on the applicable answers for each study. Scores of individual items

from the critical appraisal tool were added to present the total score out.

Quality assessment / Risk of bias analysis Collection of information was done independently by Reviewer 1 and Reviewer 2 utilizing the Cochrane Collaboration tool for risk of bias assessment including: sequence generation, allocation concealment, in complete outcome data (dropouts and withdraws), blinding and Selective outcome reporting (Appendix III) (Higgins & Green, 2011).
Description of the procedures undertaken to evaluate each domain for each study was done and rated as 'low risk' or 'high risk'. The risk of bias in a study was reported as unclear, if the details provided are inadequate. In such instances, the study investigators got contacted to provide the details. The first and second reviewers individually make the judgments for the risk of bias based on the criteria for judging for the risk of bias (Appendix IV) (Higgins & Green, 2014). Areas of disagreement were resolved via consensus or consulting with the supervisor (Prof. Sam Ibeneme).

Strategy of data synthesis The research question on the "effects of physical exercise on glycosylated hemoglobin, inflammation and neuropathic indices in diabetic conditions" was answered, with the outcome measures of the intervention presented, examined and combined in proof/evidence tables.
Proper statistical methods for different variables such as continuous variable, and weighted mean differences, were used when outcomes were consistent or standard mean differences when there was variation in outcomes with CI of 95% while for dichotomous variables, risk ratio was applied with CI of 95%. This study also included a meta-analysis which estimated the pooled effect sizes across the included studies using a random-effect model (I2) relying on the level of heterogeneity of effects of the intervention. Assessment of heterogeneity was done via the Cochrane x2 test (10% significant level) and Higgins I2 for which values of 25%, 50% and 75% show low, medium and high heterogeneity respectively, as stipulated by the guidance on the Cochrane Handbook for Systematic Reviews of interventions (Higgins & Green, 2014).

Subgroup analysis Hyphen.

Sensitivity analysis The impact or significance of studies with a high risk of bias on the general outcomes were determined via sensitivity analysis. Sub-group analyses were conducted to determine the potential influence of significant heterogeneity which could be due to the impact of the intervention types or comparators on the treatment effect direction. It was done only when there were more than two studies with homogeneous subsets. This was only performed for the primary outcome.

Language restriction The review is restricted to English language.

Country(ies) involved Nigeria.

Keywords Diabetes milletus; Gestational diabetes; Exercise; Physical activity; physical exercise; Exertion; supervised exercise; randomized; trial; : Inflammation, glycosylated haemoglobin, neuropathy.

Dissemination plans 1. Planning to publish research work.
2. Abstract submission in Scientific conference where research work would be discussed with many professionals in the field.
3. Research work presentation in seminars and workshops.

Contributions of each author
Author 1 - Glory Chigbundu - Is the first reviewer, topic formulation, literature search, search strategy formulation, data screening (title, abstract and full text) and data synthesis were conducted by the reviewer.
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