Protocol

Comparison of the Effectiveness of Metformin with Lifestyle Modification for the Primary Prevention of Type 2 Diabetes: A Protocol for Systematic Review and Meta-Analysis

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REGISTRATION NUMBER: PROSPERO CRD42021237135.

Abstract

Background: Almost 90% of people with diabetes have type 2 diabetes and the upward trend of this chronic disease is still ongoing, so that after about four decades, this disease is still one of the top 10 causes of death, while half of these deaths occur in people under 60 years of age. Therefore, prevention is essential and the implementation of the most effective intervention approach is required after recognizing at-risk individuals. This study aimed to evaluate the effect of lifestyle modification interventions and metformin on the prevention of type 2 diabetes and improvement in four risk factors related to diabetes.

Methods: The study was conducted by searching PubMed, Scopus, Web of science, and Google Scholar without time and language restrictions. Randomized controlled trials which examined the effect of both lifestyle modification interventions and metformin in a population over the age of 18 years with no history of any type of diabetes were included. After the withdrawal of poor quality studies and those withfollow-up time of less than 6 months, structured review and meta-analysis will be performed to calculate the relative risk of type 2 diabetes incidence and mean difference in weight, body mass index, plasma fasting glucose, and hemoglobin A1c. Data analysis was performed using comprehensive meta-analysis software version 2.2.064.

Conclusion: This study will make it possible to choose between two conventional therapeutic approaches (lifestyle modification and metformin) to prevent type 2 diabetes and its impact on four risk factors.

Keywords: Diabetes, Lifestyle Modification, Metformin, Primary Prevention, Systematic Review, Meta-Analysis.

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Introduction

The world health organization (WHO) warning about the worldwide ascending trend of diabetes prevalence took place for the first time in 1980 with the report of 108 million affected people [1]. It is predicted that 700 million people that is equal to the 10.9% of the adult population (20-79 years old) will develop diabetes by 2045. In Iran, it is estimated that the number of people with diabetes is approximately 5 million and this number will be almost doubled by 2040. Approximately, 90% of all patients with diabetes are affected by type 2 diabetes [2]. Even after four decades, diabetes is still among the 10 main leading reasons of mortality, while half of these deaths happen in people under the age of 60 years old [3]. The increasing incidence of type 2 diabetes in adolescents in recent years, with the increase in

their longer survival, has led to an increase in the overall prevalence of type 2 diabetes [4]. Given that the incidence is not affected by the time and survival of individuals, it can be a more valuable measure for preventative interventions in the population [5].

The high prevalence of diabetes has a significant economic impact on individuals and governments [6]. A complicated collection of genetic, environmental, demographic, and socioeconomic factors has led to an increase in the number of patients with diabetes. The phenomenon of urbanization and consequent decrease in the level of physical activity, the increase in overweight, and obesity as the population gets old, are among the causes of increased prevalence of diabetes [3]. Obesity and overweight are two strong risk factors for diabetes that account for a large proportion of the burden of diabetes in the world and are strongly associated with unhealthy lifestyle [4]. Given that obesity increases the risk of diabetes, studies have shown that plasma glucose levels decrease by losing weight, so that a 10% reduction in body weight in obese people can significantly improve glucose tolerance [7, 8].

According to review studies, two effective methods in preventing diabetes are lifestyle modification and medication [9, 10]. One of the characteristics of these two methods is the availability and the security [11]. Metformin affects hepatic glucose production by potentiating insulin activity in the liver, reducing fasting glucose, and reducing the risk of type 2 diabetes in people with pre-diabetes [12, 13]. Lifestyle modification based on low fat diet, weight loss and physical activity can be effective in better control of blood sugar and prevention of diabetes [14, 15]. The aim of this study was to answer the research question "which of the two lifestyle modification interventions and metformin in adults will be more effective in preventing type 2 diabetes and changes in weight, body mass index (BMI), plasma fasting glucose (FPG), and hemoglobin A_1c (HbA_1c) factors?"

Materials and Methods

This protocol is reported based on PRISMA-P guideline [16]. This review was based on the randomized controlled trial (RCT) studies.

Inclusion criteria

The search strategy and selection criteria for studies are based on population, intervention, comparison and outcome (PICO) [17]. RCT studies targeting the population over the age of 18 years without diabetes or cardiovascular disease and do not take metformin were selected. The intervention groups included lifestyle modification intervention based on therapeutic lifestyle change (TLC) and diabetes prevention program (DPP), and metformin intervention. Then, people participating in these two groups were directly compared. The primary outcome of this study is the development of type 2 diabetes and the secondary outcomes are body weight, body mass index (BMI), fastilng plasma glucose (FPG), and hemoglobin A1c (HbA1c).

Information Sources

Search strategy was designed and performed without any time or language restrictions in PubMed, Scopus, Web of science, and Google Scholar databases to find relevant papers with combination of keywords, including diabetes, primary prevention, lifestyle, and metformin. Structured search terms were the words related to the subject and medical subject headings (MESH). After trying different strategies, the search strategy was selected with the least filter used and the least restriction.

The draft search strategy for the PubMed database conducted on 1/25/2020 is as follows:

((("Diabetes Mellitus, Type 2"[MeSH Terms] OR diabetes[Title/Abstract]) OR prediabetes[Title/Abstract] OR NIDDM[Title/Abstract]) AND ("life style"[MeSH Terms] OR lifestyle[Title/Abstract] OR lifestyles[Title/Abstract] OR "lifestyle intervention"[Title/Abstract] OR "lifestyle

modification"[Title/Abstract] OR "lifestyle change"[Title/Abstract] OR "therapeutic lifestyle change"[Title/Abstract] OR "way of acting"[Title/Abstract] OR "style of living"[Title/Abstract] OR "way of life"[Title/Abstract] OR "manner of living"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "Therapeutic Lifestyle Changes" [Title/Abstract] OR Exercise[tiab] OR diet*[Title/Abstract] OR nutrition[Title/Abstract] OR food[Title/Abstract] OR eating[Title/Abstract] OR dietary[Title/Abstract] OR dietetic[Title/Abstract] OR activity*[Title/Abstract] OR DPP[Title/Abstract] OR TLC[Title/Abstract]) AND (metformin[MeSH Terms] OR metformin[Title/Abstract] OR glucophage[Title/Abstract] OR N,N-dimethylbiguanide[Title/Abstract]) AND (prevention[Title/Abstract] OR Incidence[MeSH Terms] OR incidence[tiab] OR risk [tiab] OR incident[tiab] OR occur [tiab] OR occurs[tiab] OR occurrence[tiab] OR "prevention & control"[Title/Abstract] OR "chronic disease prevention"[Title/Abstract] OR "prevention program"[Title/Abstract] OR "incidence density"[Title/Abstract] OR "incidence rate"[Title/Abstract] OR "diabetes prevention program"[Title/Abstract] OR "diabetes prevention"[Title/Abstract]))).

After preparing the initial list of articles, using EndNote software version X8.0.1, the title of review articles and duplicates will be removed first. Then the title and abstract of the remaining articles will be carefully studied. Then, the full text of the review articles and finally the qualified articles will be selected. The search was conducted separately by two project partners in the mentioned databases with the determined search strategy, and any disagreement in this field was resolved through discussion with the third researcher.

Extracting the data

The eligible articles and information about the author's name, year of publication and year of study, source, mean age and sex of participants, place of study, type of study, sample size, duration of follow-up of participants, more detailed information on lifestyle modification interventions and metformin use, information about the effect size for outcomes including the incidence of type 2 diabetes, body weight, BMI, FPG, and HbA1c, and criteria for detecting these variables will be entered in the Excel file. Information will be extracted to compare the impact of these two intervention methods.

Criteria for diagnosing pre-diabetes and diabetes

The WHO criteria in 1980: fasting blood sugar (FBG)> 140 mg/dL and impaired glucose tolerance (IGT) and oral glucose tolerance test (OGTT) 140-199 mg/dL. The WHO criteria in 1985: normal blood sugar is not defined, FBG> 140 mg/dL and IGT and OGTT 140-200 mg/dL are normal and impaired fasting glucose (IFG) is not defined. The WHO criteria were not found in 1994. The WHO standards in 1999 defined FBG <110 mg/dL as normal, IGT was defined as FBG <126 mg/dL, and OGTT 140-200 mg/dL; Impaired fasting glucose (IFG) is also defined as FBG 110-126 mg/dL and OGTT<140.

American diabetes association (ADA) criteria in 1997 were FBG <110 mg/dL and OGTT<140 mg/dL as normal; IGT is defined by the OGTT test as 140-200 mg/dL, IFG as FBG 110-126 mg/dL. The 2003 ADA standard defined FBG <110 mg/dL and OGTT <140 as normal; it also defines IGT with OGTT 140-200 mg/dL and IFG with FBG 100-124 mg/dL. The ADA criteria for 2008 were FBG <100 mg/dL and OGTT <140 mg/dL as normal; IGT is defined by OGTT 140-199 mg/dL and IFG is defined by FBG 100-125 mg/dL; diabetes is also defined by FBG>125 mg/dL and OGTT>200 mg/dL. The ADA criteria in 2010 were pre-diabetes HbA1c 5.7-6.4%, FBG 5.6-6.9 mmol/L and 2hrGTT 7.8-11.0 mmol/L and diabetes is defined as HbA1c> 6.5% or FBG> 7.0 mmol/L or 2hrGTT>11.1 mmol/L.

Interventions

Lifestyle: The lifestyle is the normal way of life and culture of an individual or group. Lifestyle modification is one of the most important ways to promote health [18]. In the field of lifestyle modification, two approaches of the TLC and DPP were considered. TLC, which focuses on lowering blood cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, is part of the National Cholesterol Education Program (NCEP) and Adult Therapy Panel (ATP) [19]. The third report of this specialized panel aimed to diagnose, evaluate, and treat blood cholesterol in adults through diet which focuses on weight management and increased physical activity [20]. The report, based on extensive trials and evidence-based studies over several decades, showed a strong link between high blood cholesterol and the risk of cardiovascular disease, and emphasizes the TLC approach as a treatment for high-risk individuals [19]. In the TLC diet, 20-35% of calories are received from fat, 50-60% from carbohydrates, and 15-25% from protein. It also recommended moderate to vigorous physical activity for at least 30 minutes to prevent chronic diseases and 60-90 minutes to lose weight [20]. The two main goals in the DPP lifestyle protocol are to lose 7% of body weight and perform 150 minutes of physical activity per week. Lifestyle trainers train and motivate people by holding 16 group sessions and through frequent contacts with individuals monitoring the strict implementation of the protocol [21]. Weight loss and physical activity are the two main pillars of lifestyle modification to prevent type 2 diabetes and better control blood sugar in patients with diabetes. According to meta-analysis studies, lifestyle interventions can reduce the incidence of type 2 diabetes by approximately 50% compared to standard medical recommendations [14].

Metformin: Metformin is prescribed in various doses to prevent or delay the progression of pre-diabetes to type 2 diabetes, to prevent or reverse the process of insulin resistance and / or β-cell dysfunction associated with maintenance of dysglycemia [22]. Studies have shown that metformin reduces hepatic glucose production by enhancing insulin activity in the liver [13]. Another therapeutic function of metformin is to improve insulin activity in skeletal muscle, which plays the key role in increasing non-oxidative glucose excretion [23].

Outcomes

Type 2 diabetes: It is a chronic disease (1) defined by varying degrees of poor β cell function and insulin resistance; occurring when the body is unable to use the insulin produced effectively [24].

Body weight: It is the body weight of people measured in kilograms.

BMI: According to the WHO definition, a person's weight is measured in kilograms divided by height in meters, and indicates the body fat index in adults, and excess fat is associated with disease and death.

FPG: It is a blood test taken after 8 hours of fasting. If the result is abnormal, the diagnosis is impaired fasting glucose.

HbA1c: It is a measure of glycated hemoglobin, which reflects glucose concentration over two to three months. The accuracy of the test is due to the disorder in hemoglobinopathies.

Evaluating the quality of the selected studies

The quality of RCT studies will be evaluated according to Jadad criteria [25]. This criterion gives a maximum of 5 points according to the three key characteristics of randomization, blindness, and the rate of loss and response of participants in clinical trials [26].

Data synthesis and statistical analysis

Numbers related to the effect size of type 2 diabetes and the four risk factors (Means and their corresponding standard deviation (SD), risk ratio (RR) / odds ratio (OR)) will be extracted from the articles and finally the random-effects model will be used to derive the pooled effect

sizes. Since the standard deviation was not reported directly, the standard error (SE) according to this formula: $SD = SE \times \sqrt{n}$ was used. Cochran's Q test and I^2-index will be used to investigate statistical heterogeneity among the studies presented in the meta-analysis. The range of I^2 is from 0 to 100. The I^2 between 0 and 25, limited or no heterogeneity is indicated, I^2 between 25-50 indicates a weak heterogeneity, I^2 between 50-75 indicates a relatively high heterogeneity, and I^2 between 75 to 100 indicates a high heterogeneity. In the Cochran (Q) test, the P-value less than 0.1 is considered as a significant heterogeneity [27]. Then, if a significant heterogeneity is observed between the above studies, meta regression analysis or subgroups will be used to find the factors that have caused this heterogeneity[28]. If heterogeneity is detected, the random effects model will be used; otherwise, the fixed effects model was used [28]. It should be noted that in case of having more than one OR / RR in each study, the OR / RR with a more complete adjustment was used. The impact of applied studies quality should be assessed regularly in meta-analyses and systematic reviews. this would be perfectly achieved by performing sensitivity analysis [28]. If the incidence rate in the study intervention groups was zero, we would assume the value of incidence rate one in the meat-analysis. Then, high-quality studies and follow-up time of more than 6 months will be selected and categorized based on the intended outcomes of this review, and meta-analysis was performed on the effect size of the studies. The data analysis will be performed using comprehensive meta-analysis (CMA) software version 2.2064.

Meta-analysis evaluation

Egger's test, trim and fill, as well as visual evaluation with funnel diagrams will be used to measure emission bias by CMA software. In this regard, a p-value greater than 0.05 indicated no diffusion bias.

Evaluating power of evidence

The grading of recommendations, assessment, development, and evaluations (GRADE) tool will be used to ensure the quality of the obtained evidence [25]. The evaluation approach will be based on summary findings and quality evaluation [26]. The quality of evidence will be assessed in the areas of risk of bias, effect size stability, directness, accuracy, and bias in dissemination [29]. Then, the quality will classified into four levels, including high, medium, low, and very low [30].

Discussion

This systematic review and meta-analysis will aim to make a direct comparison between the two lifestyle modification interventions and the common drug metformin in preventing type 2 diabetes. However, in addition to the initial outcome of type 2 diabetes, the consequences of body weight, BMI, FPG, and HbA1c will also investigated. Previous studies have indirectly compared lifestyle modification intervention and other pharmacological and placebo methods in the prevention of diabetes, but this study directly compares these two intervention approaches and the four modifiable risk factors associated with diabetes. The advantage of the present meta-analysis is that the search strategy will be performed without any time and language restrictions. Reviewing only randomized trial studies with a follow-up period of more than 6 months reduced heterogeneity. One of the limitations of the study can be the difference in the criteria for diagnosing diabetes as well as the types of lifestyle modification interventions and metformin. Therefore, in line with the diabetes prevention and control program, identifying people at risk and intervention measures are necessary and cost-effective. This study will review RCT studies to find the best approach to prevent type 2 diabetes and its four associated risk factors to make an accurate comparison of the two approaches for prescribing metformin and changing or modifying lifestyles; since after

identifying people at risk, planning is required for intervention.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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