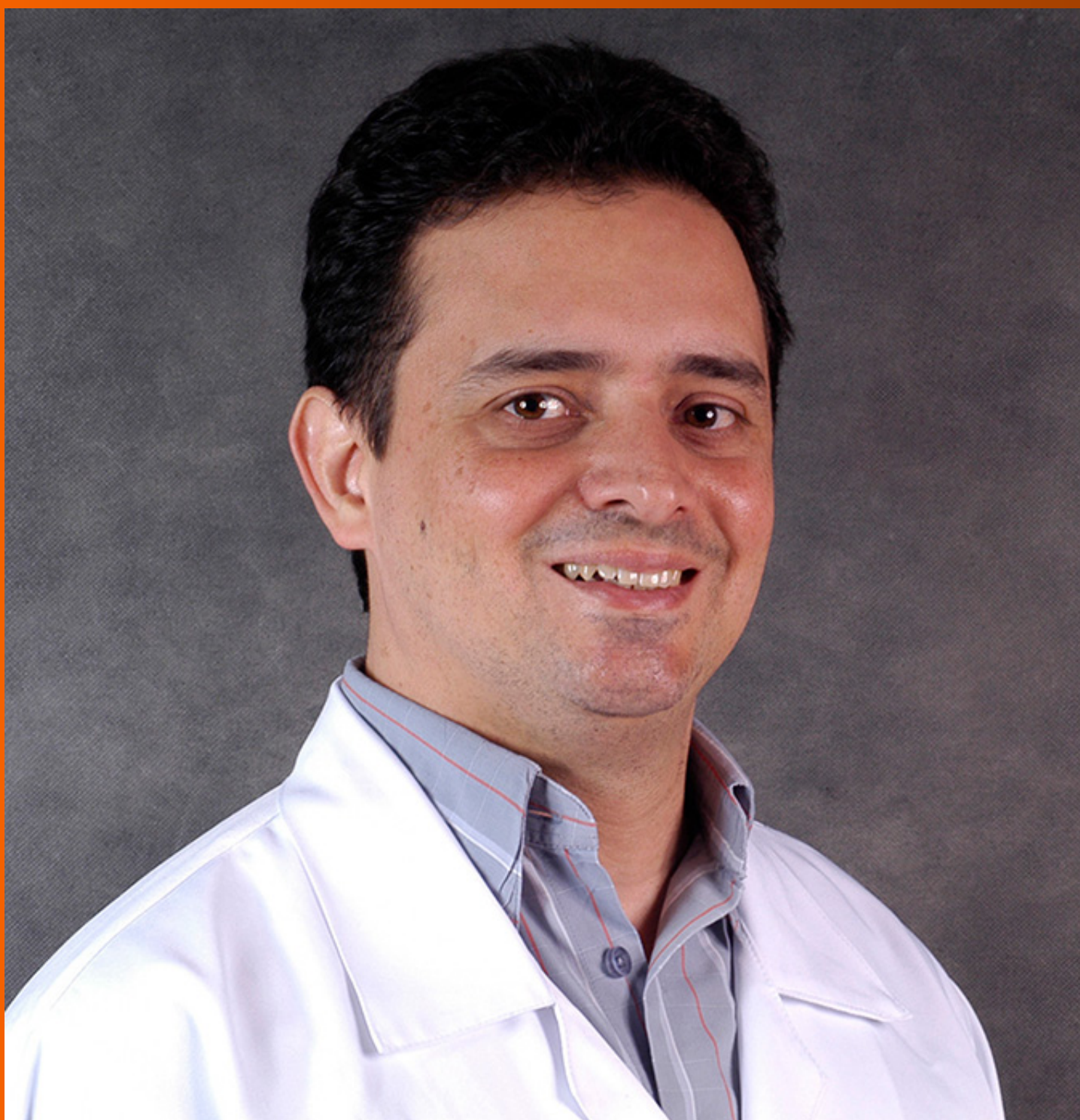


World Journal of *Diabetes*

World J Diabetes 2023 May 15; 14(5): 447-631



REVIEW

- 447 Inter-relationships between gastric emptying and glycaemia: Implications for clinical practice
Arunachala Murthy T, Chapman M, Jones KL, Horowitz M, Marathe CS
- 460 Early diabetic kidney disease: Focus on the glycocalyx
Yu H, Song YY, Li XH
- 481 Diabetes mellitus type 2 as an underlying, comorbid or consequent state of mental disorders
Borovcanin MM, Vesic K, Petrovic I, Jovanovic IP, Mijailović NR
- 494 Mechanism of immune attack in the progression of obesity-related type 2 diabetes
Wang HW, Tang J, Sun L, Li Z, Deng M, Dai Z
- 512 Diabetes mellitus and atrial fibrillation-from pathophysiology to treatment
Leopoulou M, Theofilis P, Kordalis A, Papageorgiou N, Sagris M, Oikonomou E, Tousoulis D

MINIREVIEWS

- 528 What, why and how to monitor blood glucose in critically ill patients
Juneja D, Deepak D, Nasa P
- 539 Exercise interventions for patients with type 1 diabetes mellitus: A narrative review with practical recommendations
Martin-Rivera F, Maroto-Izquierdo S, García-López D, Alarcón-Gómez J
- 549 Diabetes and fatty liver: Involvement of incretin and its benefit for fatty liver management
Wibawa IDN, Mariadi IK, Somayana G, Krisnawardani Kumbara CIY, Sindhughosa DA
- 560 COVID-19 vaccination and diabetic ketoacidosis
Joob B, Wiwanitkit V
- 565 Exercise therapy for sarcopenia and diabetes
Lim ST, Kang S
- 573 Intermediate hyperglycemia in early pregnancy: A South Asian perspective
Punnose J, Sukhija K, Rijhwani RM
- 585 Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes
Sayedali E, Yalin AE, Yalin S

ORIGINAL ARTICLE

Retrospective Study

- 594 Association of bone turnover biomarkers with severe intracranial and extracranial artery stenosis in type 2 diabetes mellitus patients

Si SC, Yang W, Luo HY, Ma YX, Zhao H, Liu J

Randomized Clinical Trial

- 606 Efficacy of multigrain supplementation in type 2 diabetes mellitus: A pilot study protocol for a randomized intervention trial

Mohd Ariffin NA, Mohd Sopian M, Lee LK

SYSTEMATIC REVIEWS

- 617 Cardiometabolic effects of breastfeeding on infants of diabetic mothers

Elbeltagi R, Al-Beltagi M, Saeed NK, Bediwy AS

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, José Carnevalheira, MD, PhD, Associate Professor, Faculty of Medical Sciences, University of Campinas, Campinas 13083, São Paulo, Brazil. jbcc@g.unicamp.br

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

May 15, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Randomized Clinical Trial

Efficacy of multigrain supplementation in type 2 diabetes mellitus: A pilot study protocol for a randomized intervention trial

Nur Anis Mohd Ariffin, Mastura Mohd Sopian, Lai Kuan Lee

Specialty type: Integrative and complementary medicine**Provenance and peer review:** Invited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0**P-Reviewer:** Horowitz M, Australia; Mohammadi S, Iran; Moreno-Gómez-Toledano R, Spain**Received:** December 23, 2022**Peer-review started:** December 23, 2022**First decision:** February 20, 2023**Revised:** March 2, 2023**Accepted:** April 10, 2023**Article in press:** April 10, 2023**Published online:** May 15, 2023**Nur Anis Mohd Ariffin, Lai Kuan Lee**, Food Technology Division, School of Industrial Technology, Universiti Sains Malaysia, Gelugor 11800, Pulau Pinang, Malaysia**Mastura Mohd Sopian**, Oncology and Radiological Sciences Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam 13200, Pulau Pinang, Malaysia**Corresponding author:** Lai Kuan Lee, PhD, Senior Lecturer, Food Technology Division, School of Industrial Technology, Universiti Sains Malaysia, Gelugor 11800, Pulau Pinang, Malaysia. l.k.lee@usm.my

Abstract

BACKGROUND

Uncontrolled type 2 diabetes mellitus (T2DM) may lead to microvascular complications (nephropathy, retinopathy, and neuropathy) and cardiovascular diseases. The beta-glucan content in grains has the potential to improve insulin sensitivity, lowering postprandial glucose response and reducing inflammation degrees. A proper combination of grains not only satisfies human body's need, but also provides essential and reasonable nutritional contents. However, no trial has been conducted to evaluate the roles of multigrain in T2DM.

AIM

To determine the efficacy of multigrain supplementation among T2DM patients.

METHODS

From October 2020 to June 2021, a total of 50 adults living with T2DM, who were receiving standard diabetes care at Day Care Clinic, were randomized into either a supplementation group or a control group. The supplementation group received twice daily 30 g multigrain supplement (equivalent to 3.4 g beta-glucan) with standard medication for 12 wk, while the control group was prescribed with standard medication. Parameters such as glycemic control (HbA1c, FPG, and HOMO-IR), cardiometabolic profile (lipid profile, renal function test, and liver function test), oxidative stress status, nutritional status, and quality of life (QoL) were assessed at two time points: Baseline and the end of the treatment period (week 12).

RESULTS

The primary outcomes were the mean difference of glycated haemoglobin (%), fasting plasma glucose, and serum insulin as intervention effects. Secondary

outcomes included the measurement of cardiometabolic profile, antioxidative and oxidative stress status, nutritional status indices, and QoL. Tertiary outcomes involved the determination of safety and tolerability, and supplementation compliance.

CONCLUSION

The present clinical trial will reveal the effectiveness of multigrain supplementation among T2DM patients for the improvement of diabetes management.

Key Words: Beta-glucan; Clinical trial; Multigrain; Type 2 diabetes mellitus; Glycemic control

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This is the first human clinical trial aimed to evaluate the effectiveness of multigrain supplementation among type 2 diabetes mellitus patients. The changes of glycemic control, cardiometabolic profile, oxidative stress status, nutritional status, and quality of life were measured. Our study also evaluated the safety, tolerability, and compliance of the supplementation.

Citation: Mohd Ariffin NA, Mohd Sopian M, Lee LK. Efficacy of multigrain supplementation in type 2 diabetes mellitus: A pilot study protocol for a randomized intervention trial. *World J Diabetes* 2023; 14(5): 606-616

URL: <https://www.wjgnet.com/1948-9358/full/v14/i5/606.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v14.i5.606>

INTRODUCTION

Diabetes mellitus is one of the major global health problems and driving causes of morbidity and mortality around the world. Type 2 diabetes mellitus (T2DM) is a metabolic disease that causes sugar to build up in the bloodstream, characterized by insulin insensitivity as a result of insulin resistance in the muscle and adipose tissue, declining insulin production, and eventual pancreatic beta-cell failure[1]. When the beta-cells in the pancreas malfunction and/or insulin resistance develops in the liver, skeletal muscle, or adipose tissue, hyperglycemia arises, resulting in an excess level of glucose circulating in the blood[2]. T2DM has attained epidemic proportions worldwide with 415 million cases estimated globally in 2015, and the number is expected to increase dramatically in the next decades, reaching 642 million by 2040[3]. T2DM is the foremost common frame of diabetes mellitus, accounting for more than 90% of all cases of adult-onset diabetes mellitus in Malaysia[4]. According to the National Health and Morbidity Survey (2020)[5], one in every five adults in Malaysia has T2DM.

Uncontrolled diabetes mellitus may lead to microvascular complications (nephropathy, retinopathy, and neuropathy) and macrovascular complications, later leading to severe peripheral vascular disease, premature coronary artery disease, and increased risk of cerebrovascular diseases[6]. The main aim of diabetes management is targeted at reducing the acute and chronic diabetes complications, *via* the effective control of plasma glucose, blood pressure, lipid profile, and body weight concurrently[7]. The distinction between effective treatment and cure is obscured within the case of diabetes, but few individuals can reverse it through diet changes and be able to reach and maintain normal blood sugar levels without or with minimum medication. In particular, nutrition or dietary therapy is one of the trending complementary medicines, with the ultimate goal to control, prevent (occurrence), and reverse (by averting resulting complications after its onset) the disease[8].

Wholegrain is defined as consisting of the entire grain (bran, endosperm, and germ), and most fiber ingredient from the wholegrain is of insoluble origin, including the cellulose, hemicellulose, and lignin, with the exception of barley and oat (relevant sources of soluble fiber such as beta-glucan, pentoses, and arabinosyl)[9]. Wholegrain is a good source of dietary fiber, resistant starch, antioxidants, and other important micronutrients, such as folic acid and other vitamins[10]. Fiber from the wholegrain has been shown to reduce the risk of T2DM by improving insulin sensitivity, lowering postprandial glucose response, and lowering inflammation[11]. In addition, laboratory and epidemiological investigations have reported that wholegrain, especially barley and oat, contain a high amount of beta-glucan, which has been proven to lower blood glucose levels, improve glucose tolerance, ameliorate hyperlipidemia, improve immunity, and decrease infections[12]. In parallel, the demand of the multigrain source in the commercial market is increasing tremendously due to an increased awareness of managing chronic diseases by ingesting health promoting functional foods[13]. Multigrain, a proper combination of few types of grains, could satisfy human body's need with essential nutritional benefits[14].

Several published clinical trials were looking into the effect of single grain supplementation on T2DM. Li *et al*[15] have conducted a clinical trial among overweight T2DM patients, and the results revealed that using oat as a therapeutic dietary regimen for 48 wk improved the body weight and glycemic control. The similar results have been inferred[16], where rice bran as a single treatment diet improved glycemic control and lipid profile in T2DM patients after 12 wk ingestion. In fact, multigrain consumption is more reflective towards human daily consumption. To date, study investigating the role of multigrain supplementation in T2DM patients is scarce.

Hence, the aim of this randomized clinical trial was to evaluate the effect of 12-wk of high beta-glucan multigrain supplementation on glycemic control in patients with T2DM. Secondary outcomes aim to evaluate the roles of the supplementation regimen for the amelioration of cardiometabolic health, antioxidative and oxidative stress, nutritional indices, and quality of life (QoL) among the T2DM patients. Tertiary outcomes involve the determination of safety and tolerability, and supplementation compliance.

MATERIALS AND METHODS

Study design and site

This was an open-label, randomized controlled trial, with an allocation ratio for the supplement (S) *vs* control (C) group at 1:1. All patients were registered T2DM patients. Study recruitment and enrollment began on October 14, 2020, and the completion date for enrollment was June 2021. The study site was the Day Care Clinic in Universiti Sains Malaysia Bertam Medical Center. The medical center serves as the referred medical facility in the northern region of Peninsular Malaysia.

Study population

The study population included 50 T2DM patients who were receiving standard diabetes care at Day Care Clinic. Patients aged at least 18 years of age, male or female, clinically diagnosed with T2DM for at least 6 mo duration without clinically manifest complications (retinopathy, nephropathy, neuropathy, vascular diseases, and food ulcer), and currently receiving pharmacological treatment with metformin or insulin, or a combination of metformin and glibenclamide were included in the trial (Table 1). Patients with gluten intolerance were excluded as the supplement contains gluten. Participants who have involved in another supplementary program were also excluded to avoid dilution effects.

Intervention groups

The study randomized all trial subjects into either group S or group C. Group S ($n = 25$) was supplemented with daily 60 g (2 sachets, 30 g each) of high beta-glucan (equivalent to 3.4 g) multigrain supplement for up to 12 wk. This multigrain supplement (Oat King®) was sponsored by TG Ocean Health Food Industries Sdn Bhd, Malaysia. It does not contain any food additives including food preservatives, coloring, flavoring, and sweetener. The main ingredients are oat, barley, brown rice, paddy, rice flour, corn flour, red kidney bean, black bean with kernel, and soybean (Table 2). Group S was required to consume the supplement two times per day (day and night). Patients were attending to the study site to receive and replenish the supplement at baseline, week 4, and week 8. All patients continued their standard medication as prescribed before the trial participation.

Group C ($n = 25$) continued the standard medication as prescribed prior to the trial. They were reminded not to alter their habitual dietary intake and physical activity level throughout the clinical trial period.

Study visits and measurements

Five categories of study visits have been adopted in this trial: Recruitment, screening, and inform consent form signing, randomization and blinding, enrolment visit, follow-up visits, and post week-12 visit. Figure 1 illustrates the trial flowchart.

Recruitment, screening and inform consent signing

All T2DM patients were invited face to face during their routine medical follow-up in the Day Care Clinic. Patient recruitment also occurred through electronic medical record review to identify potential participants. Patients were then invited for a screening session. The research team evaluated the eligibility criteria (both inclusion and exclusion criteria) and explained the research information in detail, followed by obtaining written inform consent. The research team did not coerce or unduly influence a patient to participate in the trial. Eligible patients underwent the randomization procedure.

Randomization and blinding

To generate a random allocation sequence, a computer-generated list of random numbers was used. Simple randomization at a 1:1 allocation ratio (1 group S: 1 group C) has been applied. The allocation sequence was concealed from the investigator enrolling and assessing participants on sequentially

Table 1 Inclusion and exclusion criteria for study population

Inclusion criteria	Exclusion criteria
Chronological age 18 years and above	Liver disease, kidney disease, or haematological disorders
T2DM \geq 6 mo, stable regimen \geq 6 mo without clinically manifest complications	Active gastric or duodenal ulcer
Male or female	Psychiatric disease or mental retardation
Pharmacological treatment with metformin or insulin, or a combination of metformin and glibenclamide	Cancer and other endocrine disorders
Free from antioxidant supplements	Alcohol or drug abuse
Free from anti-inflammatory supplements	Pregnancy or lactation
	Hormone replacement therapy
	Herbal remedies
	Gluten intolerance
	Currently under another supplementary program

T2DM: Type 2 diabetes mellitus.

Table 2 Active ingredients of Oat King®

Active ingredient	Scientific name	Percentage (%)
Oat	<i>Avena sativa</i>	11.80
Brown rice	<i>Oryza sativa</i>	9.55
Paddy	<i>Oryza sativa</i>	9.38
Rice	<i>Oryza sativa</i>	6.04
Corn	<i>Zea mays</i>	6.04
Red kidney bean	<i>Phaseolus vulgaris</i>	6.04
Black bean	<i>Phaseolus vulgaris</i>	6.04
Soy bean	<i>Glycine max</i>	5.17
Barley	<i>Hordeum vulgare</i>	4.98
Wheat	<i>Triticum</i>	4.98
Wheat germ	<i>Triticum vulgare</i>	4.98
Wheat bran	<i>Triticum aestivum</i> L	4.98
Coix seed	<i>Coix-lacryma-jobi</i>	4.22
Millet	<i>Pennisetum glaucum</i>	3.50
Red rice	<i>Oryza longistaminata</i>	2.46
Black rice	<i>Zizania aquatica</i>	2.46
Black sesame seed	<i>Sesamum indicum</i>	2.46
Navy bean	<i>Phaseolus vulgaris</i>	2.46
Mung bean	<i>Vigna radiata</i>	2.46

numbered, opaque, sealed, and stapled envelopes. To prevent subversion of the allocation sequence, the name and date of birth of the participant were written on the envelope. To randomize the participants, variables such as demographic data (age, gender, and ethnicity), clinical data (years of disease, glycemic status, and the presence of diabetic-related complications), physical activity, and medication (current prescribed medications) were taken into the consideration. To determine whether the patient would be randomized into the multigrain group S or C, randomization was made by reference to a statistical series based on the random sampling number drawn up by the statistician. The details of the series were unknown to any of the investigator or the coordinator. In order to implement blinding, participants

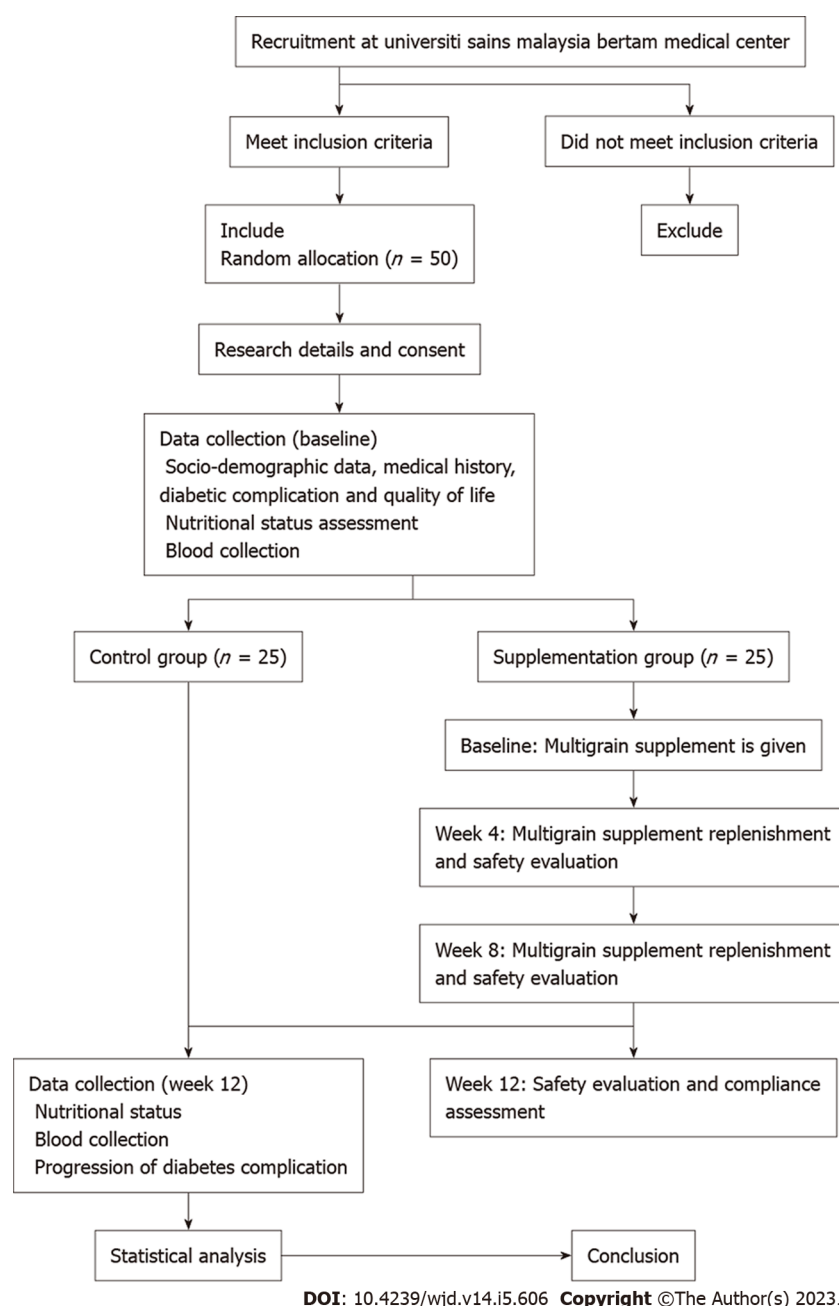


Figure 1 Flow chart of the trial.

were notified individually of the assigned group S or C. However, only data collectors, the coordinator, and the medical officer in charge of the trial were aware of the allocated arm. Investigators, data analyst, and outcome adjudicator are kept blinded to the allocation.

Enrolment visit

The enrolment visit was consisted of a semi-quantitative questionnaire, physical examination, fasting blood sampling, and laboratory tests. The semi-quantitative questionnaire gathered information with regard to the socio-demographic background and medical history (including medical prescription). Lifestyle health behaviors included alcohol use, cigarettes smoking, and routine exercise practices. Physical examination involved the measurement of systolic and diastolic blood pressure, handgrip strength, and nutritional status assessments (anthropometry and body composition measurements).

A total of 20 mL of fasting venous blood was drawn from each participant for the subsequent clinical laboratory testing. Routine laboratory testing comprised of albumin, total protein and total bilirubin, urea, minerals, uric acid, and creatinine. Fasting plasma glucose, glycated haemoglobin, serum insulin, lipid profile, and liver and kidney function tests were performed. Upon centrifugation, serum and plasma samples were collected, and the antioxidative and oxidative stress statuses were assessed *via* the measurements of total antioxidant capacity, superoxide dismutase, glutathione, glutathione peroxidase

(GPx), malondialdehyde, protein carbonyl, and 8-deoxyguanosine concentrations.

Modified diabetes QoL-17 questionnaire[17] has been used to evaluate the changes of QoL, as assessed using 7 domains (physical functioning, role limitations due to physical health, role limitations due to emotional, energy fatigue, emotional well-being, social functioning, and general health).

The supplement group received the first month supply of multigrain supplement in the form of sachet. Detail use of the supplement was elaborated, and patients returned the used sachets packaging during the follow-up visits.

Follow-up visits

Patients were evaluated at 3 study visits (Figure 2) during the week-4, week-8, and post week-12 follow-ups at Day Care Clinic. At each follow-up, the evaluation of the safety, tolerability, and compliance to the multigrain supplementation was conducted. Adverse effects concomitant to the supplementation regimen, particularly the signs and symptoms of gastrointestinal discomforts, were recorded. Compliance to the supplementation was indicated as the recorded number of consumed sachets. Replenishment of multigrain supplement was implemented during week-4 and week-8 follow-ups, respectively. Disease progression in group C was evaluated following standard medication regimen. Both the supplement and control groups were reminded not to alter their routine dietary intake and physical activity level.

Post week-12 visit

After week 12, study questionnaire, physical examination, blood profile, and QoL assessments were performed in both the supplement and control groups. In-depth interviews have been conducted by the research team members among the patients in group S. The attitudes, positive and negative perceptions towards the supplementation, and perceived general health were interviewed. All study data was recorded into the case report form.

Power and sample size calculation

The results from a previous study[18] among T2DM patients were used to determine the trial sample size. The following formula is used to calculate the trial sample size:

$$n = \frac{2 \times [Z_{(1-\alpha/2)} + Z_{(1-\beta/2)}]^2}{\Delta^2}$$

Where n = sample size, $Z = 0.8416$ (for each arm, a setting of 80% power and 95%CI was used), $Z = 1.96$, and Δ^2 = mean difference or standard deviation. Thus, for this study, $n = 18$ subjects for each arm. With the consideration that the dropout rate was 20%, the needed sample size was 22 patients for each arm.

Statistical analysis

Data analysis in the form of intention to treat will be performed at the end of the study. All statistical analyses will be implemented using the Statistical Package for Social Science (SPSS Inc., Chicago, IL, United States) software. The following statistical methods will be applied:

Assumptions will be checked for normality tests, and transformation will be applied as corrective procedures.

For descriptive statistics, categorical and continuous data, results will be presented as percentages, means with standard deviations, median and range.

For inferential tests, $P < 0.05$ will be used to indicate statistical significance (type I error) (two-tailed).

Analysis of the primary, secondary, and tertiary outcomes will be measured using Pearson's correlation, multivariate regression, repeated measures mixed models, logistic regression, and generalized linear models.

Ethics

The present study is conducted in accordance to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects have been approved by the Human Research Ethics Committee of Universiti Sains Malaysia (No: USM/JEPeM/20030183). Written consent is obtained from all patients, and the study has been registered in the clinical trial registry (ClinicalTrials.gov), with the registration ID: NCT04597229.

Study outcomes and measures

The patients' outcome measure has been assessed at two time points: Enrolment (baseline), and at the end of the treatment period (post week-12).

The primary outcomes were the changes in fasting plasma glucose, HbA1c, and serum insulin from enrolment to post week-12, and the differences in these changes between the two study arms.

Secondary outcomes include the measurement of lipid profile, liver function test and kidney function test comparing between the study groups. The change of nutritional status, antioxidative status, and oxidative stress biomarkers were assessed too.

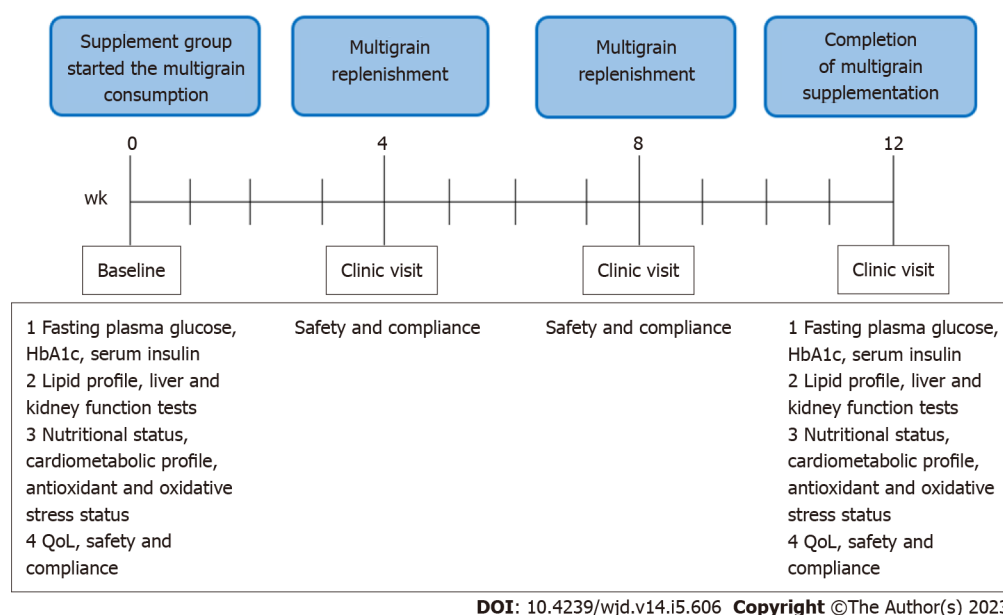


Figure 2 Supplementation administration and follow-up assessment.

Tertiary outcomes were the change in QoL, and the difference in this change between the study groups. In term of safety evaluation, a list of gastrointestinal discomfort symptoms has been assessed among the participants in the supplementation group. The intensity of the gastrointestinal symptoms is defined as none, mild, moderate, severe, and very severe according to the symptoms (bloating, abdominal rumbling, flatulence, abdominal pain, nausea, vomiting, heart burn, loss of appetite, diarrhea, and constipation). Patients who showed symptoms have been referred to the physician in charge. Compliance to the supplementation regimen was assessed by counting the number of the consumed sachets during every follow-up visit (week-4, week-8, and week-12). Patients were asked to provide the reason for missed sachet consumption.

RESULTS

No result is provided as this is a pilot study protocol for a human clinical trial.

DISCUSSION

The current randomized control trial is aimed to evaluate the effects of multigrain supplementation as a complementary regimen *vs* a control (without supplementation) among patients with T2DM over a period of 12 wk. For the past decades, the underlying mechanisms for an association between grains and T2DM are not entirely clear, but grains may lower the risk of T2DM by improving insulin sensitivity[19]. Particularly, the potency of medium glycemic index multigrain flour to reduce glycemia in T2DM has been highlighted for the implementation of a better dietary plan for diabetes control[20]. Our study is designed to determine if multigrain supplementation, instead of single grain diet, is effective to ameliorate T2DM. Multigrain consumption is relatively a 'pure' dietary routine for human being.

Beta-glucan, pentose, and arabinoxylan are found in wholegrain fiber, especially in barley and oats, and other insoluble fibers, including cellulose, hemicellulose, and lignin[21]. These components play a vital role in a collective way, by improving the glycemic metabolism and reducing T2DM risk factor. Soluble fiber from oats and barley (with 3 g of beta-glucan intake per day) has been found to be effective in lowering total cholesterol and low-density lipoprotein (about 5% to 10% reduction, respectively)[15]. The latest finding also outlined the possible role of minimally processed whole grains over 2 wk in improving measures of glycemia in free-living adults with T2DM[22]. In addition, beta-glucan is evident to increase the intestinal viscosity, decrease the starch digestion, and reduce the food intake by increasing satiety, reducing hyperglycemia, lowering the lipid profile, and reducing weight[23].

Grains are generally high in magnesium. Magnesium is an essential co-factor for many enzymes, including the enzymes involved in glucose and insulin metabolism. Grain also contains a group of phenolic compounds, the avenanthramides. Avenanthramides are antioxidant and can enhance endothelial functions and anti-inflammatory properties[24]. Another potential antioxidant found in

grains is vitamin E. Vitamin E is an intracellular antioxidant, which prevents the oxidative damage of the polyunsaturated fatty acids in cell membranes. Vitamin E also facilitates to remain selenium in a reduced state[25]. Selenium plays an important role as a potent antioxidant. For example, GPx reacts with hydrogen peroxide to prevent harmful free radicals, DNA damage, and the formation of metabolic active carcinogens[26]. High selenium levels may help to reduce the formation of oxidized low-density lipoprotein (LDL) cholesterol and, as a result, reduce the risk of heart disease[27] and inflammation, strengthen the immune system in the body[28], and prevent the incidence of cancer[29]. Collectively, micronutrients in grains have their own beneficial roles to reduce the risk of T2DM complications.

In addition, bioactive compounds present in grains (such as phenolic compounds, phytosterols, betaine, and carotenoids) can help to improve insulin sensitivity and slow the progression of T2DM[30]. Bioactive compounds act by reducing the oxidative stress, inflammatory cytokine transcription, and subclinical inflammation[31] since increased oxidative stress seems to be a harmful component contributing to worsening insulin resistance and beta-cell dysfunction, which may lead to T2DM complications[32]. A previous study showed that a diet rich in polyphenols increased glucose tolerance and insulin sensitivity, and reduced the postprandial triglyceride response[33]. Moreover, phytosterols are known to be effective to reduce LDL cholesterol, as consumption of 2 g of plant sterol from wholegrain resulted in a 5.6% reduction in LDL cholesterol among T2DM patients after 4 wk ingestion [34]. Indirectly, this may reduce the risk of diabetes complications, particularly macrovascular complications.

Grain plays a significant role in reducing the energy intake. It has lower energy density, and the larger starch granules significantly contribute to a greater chewing rate, hence increasing satiation[10,35,36]. Fiber from the grain also increases gastric distension and delay the intestinal transit time, contributing to the stimulation of satiety signals[37] and increasing hormones levels involved in the energy homeostasis and plasma glucose control[38]. This process involves the stimulation of satiety signal in the brain, where body weight regulation hormones, ghrelin, peptide YY, cholecystokinin, gastric inhibitory polypeptide, and glucagon-like peptide 1 are regulated as part of the energy homeostasis and plasma glucose control[39]. This process might have a positive impact due to the change in gut microbiota profile[40,41] and cause a decrease in subclinical inflammation. Similarly, the slower process of carbohydrate digestion, as well as the glucose and free fatty acid absorption in the intestine[42], reduces insulin demand and stimulates fat oxidation, thus contributing to the reduction of fat storage[20]. Collectively, the synergistic mechanisms result in an increase in the hypothalamic satiety signal in the brain[20], which further leads to the body weight reduction and energy homeostasis, as well as glucose control[10,43-45].

Strengths of this study include a randomized controlled trial design, where the covariates could be equally distributed. The multigrain powder is formulated using commonly consumed grains, thus omitting the issues of food safety concern. Regular follow-up on a monthly basis allowed close monitoring of supplement adherence. The trial also included detail measurements of nutritional status, antioxidative status, oxidative stress biomarkers, and QoL, which allowed better result interpretation. These analyses will inform whether any potential effect extends to other metabolic or peripheral parameters. We acknowledge the small sample size of the study as the major limitation for this pilot clinical trial.

Important implications are expected from this research regardless of the findings. In a condition where beneficial effect is supported by evidence of a positive effect on long-term blood glucose levels, public health efforts should be undertaken to encourage the consumption of multigrain as functional foods. Contradictorily, if a beneficial effect is not supported, this could suggest that multigrain does not translate into strong long-term benefits for blood glucose control under daily conditions.

CONCLUSION

This is a pioneer, pilot clinical trial that aims to evaluate the efficacy of high beta-glucan multigrain supplementation among T2DM patients. Important trial outcomes, such as glycemic control, peripheral antioxidative capacity, cardiometabolic health, nutritional status, QoL, safety, and compliance have been studied extensively. The results of the trial are important to suggest a scientifically driven complementary dietary agent for better management of T2DM.

ARTICLE HIGHLIGHTS

Research background

Type II diabetes mellitus (T2DM) has emerged as a major public health challenge around the world. Diet is a major lifestyle factor that can greatly influence the incidence and progression of T2DM. The notion that foods not only provide basic nutrition but can also prevent diseases and ensure good health and longevity is now attaining greater prominence.

Research motivation

Typically, grains, with its rich non-starch polysaccharides content, are receiving concern among the scientific communities. Multigrain is rich with thiamine, riboflavin, pantothenic acid, iron, zinc, and copper, and it can be prepared using different preparation processes, which usually comprises a high amount of dietary fiber content. Multigrain consumption is indeed a more representative dietary intervention as compared to single grain intake. There is a need to examine whether supplementation with multigrain, a more representative dietary regimen to human routine consumption pattern, would yield better outcomes among T2DM patients.

Research objectives

The objectives of the present study were to evaluate the effects of multigrain supplementation on glycemic control, cardiometabolic profile, oxidative stress, nutritional status, and quality of life (QoL) among T2DM patients. The safety, tolerability, and adherence of the supplementation were evaluated.

Research methods

Fifty T2DM patients have been randomly assigned to receive either 60 g multigrain supplementation (containing 3.4 g beta-glucan) coupled with prescribed standard medication regimen ($n = 25$), or standard medication regimen alone ($n = 25$) for 12 wk. Study outcomes involved the changes of glycemic control, cardiometabolic profile, oxidative stress, nutritional status, and QoL.

Research results

No result is provided as this is a pilot study protocol for a human clinical trial.

Research conclusions

This is a pioneer, pilot clinical trial that aims to evaluate the efficacy of high beta-glucan multigrain supplementation among T2DM patients. Important trial outcomes, such as glycemic control, peripheral antioxidative capacity, cardiometabolic health, nutritional status, QoL, safety, and compliance, have been studied extensively. The results of the trial are important to suggest a scientifically driven complementary dietary agent for better management of T2DM.

Research perspectives

The findings are expected to contribute and expand the fundamental mechanism of the role of multigrain as a complementary management agent in diabetic physiology.

ACKNOWLEDGEMENTS

We would like to thank the participation from all patients, technical staff, and staff nurses. Special thanks to Universiti Sains Malaysia for providing the support in the study.

FOOTNOTES

Author contributions: Mohd Ariffin NA, Mohd Sopian M, and Lee LK were responsible for the study conception and design, data acquisition, analysis, and interpretation, and manuscript drafting; Mohd Ariffin NA and Lee LK critically reviewed and revised the article for important intellectual content of the manuscript; all authors reviewed and approved the final version of the manuscript to be published.

Institutional review board statement: The study was reviewed and approved by the Human Research Ethics Committee of Universiti Sains Malaysia (No: USM/JEPeM/20030183).

Clinical trial registration statement: This study is registered in the clinical trial registry (ClinicalTrials.gov), with the registration ID: NCT04597229.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: (Oat King®) was funded by TG Ocean Health Food Industries Sdn Bhd to Lai Kuan Lee. Nevertheless, the funder has no role in the conduct of the research, including the study design, data collection, analysis, and interpretation, preparation of the article, and in the decision to submit the article for publication. Mohd Ariffin NA and Mohd Sopian M declare no competing interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Malaysia

ORCID number: Nur Anis Mohd Ariffin 0000-0002-1625-588X; Mastura Mohd Sopian 0000-0001-6618-8657; Lai Kuan Lee 0000-0003-0638-0799.

S-Editor: Zhang H

L-Editor: Wang TQ

P-Editor: Zhang H

REFERENCES

- 1 Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol (Lausanne)* 2013; **4**: 37 [PMID: 23542897 DOI: 10.3389/fendo.2013.00037]
- 2 Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018; **14**: 88-98 [PMID: 29219149 DOI: 10.1038/nrendo.2017.151]
- 3 Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; **128**: 40-50 [PMID: 28437734 DOI: 10.1016/j.diabres.2017.03.024]
- 4 Sami W, Ansari T, Butt NS, Hamid MRA. Effect of diet on type 2 diabetes mellitus: A review. *Int J Health Sci (Qassim)* 2017; **11**: 65-71 [PMID: 28539866]
- 5 National Institutes of Health Ministry of Health Malaysia. National Health and Morbidity Survey 2019: Non-Communicable Diseases: Risk Factors and other Health Problems. 2020. [cited 29 April 2021]. Available from: <http://bit.ly/NHMS2019>
- 6 Galicia-Garcia U, Benito-Vicente A, Jebara S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* 2020; **21** [PMID: 32872570 DOI: 10.3390/ijms21176275]
- 7 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2003; **26** Suppl 1: S33-S50 [PMID: 12502618 DOI: 10.2337/diacare.26.2007.s33]
- 8 Koithan M, Devika J. New Approaches to Nutritional Therapy. *J Nurse Pract* 2010; **6**: 805-806 [PMID: 21076654 DOI: 10.1016/j.nurpra.2010.07.001]
- 9 Kyrø C, Tjønneland A, Overvad K, Olsen A, Landberg R. Higher Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes among Middle-Aged Men and Women: The Danish Diet, Cancer, and Health Cohort. *J Nutr* 2018; **148**: 1434-1444 [PMID: 30016529 DOI: 10.1093/jn/nxy112]
- 10 Della Pepa G, Vetrani C, Vitale M, Riccardi G. Wholegrain Intake and Risk of Type 2 Diabetes: Evidence from Epidemiological and Intervention Studies. *Nutrients* 2018; **10** [PMID: 30213062 DOI: 10.3390/nu10091288]
- 11 Wirstrom T, Hilding A, Gu HF, Östenson CG, Björklund A. Consumption of whole grain reduces risk of deteriorating glucose tolerance, including progression to prediabetes. *Am J Clin Nutr* 2013; **97**: 179-187 [PMID: 23235198 DOI: 10.3945/ajcn.112.045583]
- 12 Niu M, Hou GG, Kindelspire J, Krishnan P, Zhao S. Microstructural, textural, and sensory properties of whole-wheat noodle modified by enzymes and emulsifiers. *Food Chem* 2017; **223**: 16-24 [PMID: 28069118 DOI: 10.1016/j.foodchem.2016.12.021]
- 13 Jing Q, Yingguo L, Yuanhui W, Jie C, Panfeng H. Formula and quality study of multigrain noodles. *Grain Oil Sci Technol* 2018; **1**: 157-162 [DOI: 10.3724/sp.j.1447.gost.2018.18051]
- 14 Dedeepiya VD, Sivaraman G, Venkatesh AP, Preethy S, Abraham SJ. Potential effects of nihi glucan as a food supplement for diabetes mellitus and hyperlipidemia: preliminary findings from the study on three patients from India. *Case Rep Med* 2012; **2012**: 895370 [PMID: 23304164 DOI: 10.1155/2012/895370]
- 15 Li X, Cai X, Ma X, Jing L, Gu J, Bao L, Li J, Xu M, Zhang Z, Li Y. Short- and Long-Term Effects of Wholegrain Oat Intake on Weight Management and Glucolipid Metabolism in Overweight Type-2 Diabetics: A Randomized Control Trial. *Nutrients* 2016; **8** [PMID: 27618090 DOI: 10.3390/nu8090549]
- 16 Cheng HH, Huang HY, Chen YY, Huang CL, Chang CJ, Chen HL, Lai MH. Ameliorative effects of stabilized rice bran on type 2 diabetes patients. *Ann Nutr Metab* 2010; **56**: 45-51 [PMID: 20016147 DOI: 10.1159/000265850]
- 17 Acharya LD, Shaista K, Ashan FK, Surulivelrajan M. Development and validation of quality of life assessment instrument for diabetic patients. *Asian J Pharm Health Sci* 2014; **4**: 1114-1120
- 18 Vuksan V, Whitham D, Sievenpiper JL, Jenkins AL, Rogovik AL, Bazinet RP, Vidgen E, Hanna A. Supplementation of conventional therapy with the novel grain Salba (*Salvia hispanica* L.) improves major and emerging cardiovascular risk factors in type 2 diabetes: results of a randomized controlled trial. *Diabetes Care* 2007; **30**: 2804-2810 [PMID: 17686832 DOI: 10.2337/dc07-1144]

- 19 **Pereira MA**, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL, Seaquist ER. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* 2002; **75**: 848-855 [PMID: [11976158](#) DOI: [10.1093/ajcn/75.5.848](#)]
- 20 **Bach Knudsen KE**, Hartvigsen ML, Hedemann MS, Hermansen K. Mechanisms Whereby Whole Grain Cereals Modulate the Prevention of Type 2 Diabetes. In: Mauricio D. Molecular Nutrition and Diabetes: A Volume in the Molecular Nutrition Series 2016; 87-103 [DOI: [10.1016/B978-0-12-801585-8.00008-7](#)]
- 21 **Sobhana PP**, Kandlakunta B, Nagaraju R, Thappatla D, Epparapalli S, Vemula SR, Gavaravarapu SRM, Korrapati D. Human clinical trial to assess the effect of consumption of multigrain Indian bread on glycemic regulation in type 2 diabetic participants. *J Food Biochem* 2020; **44**: e13465 [PMID: [33006193](#) DOI: [10.1111/jfbc.13465](#)]
- 22 **Åberg S**, Mann J, Neumann S, Ross AB, Reynolds AN. Whole-Grain Processing and Glycemic Control in Type 2 Diabetes: A Randomized Crossover Trial. *Diabetes Care* 2020; **43**: 1717-1723 [PMID: [32424022](#) DOI: [10.2337/dc20-0263](#)]
- 23 **Fardet A**. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr Res Rev* 2010; **23**: 65-134 [PMID: [20565994](#) DOI: [10.1017/S0954422410000041](#)]
- 24 **Lyly M**, Liukkonen KH, Salmenkallio-Marttila M, Karhunen L, Poutanen K, Lähteenmäki L. Fibre in beverages can enhance perceived satiety. *Eur J Nutr* 2009; **48**: 251-258 [PMID: [19306033](#) DOI: [10.1007/s00394-009-0009-y](#)]
- 25 **Hou Q**, Li Y, Li L, Cheng G, Sun X, Li S, Tian H. The Metabolic Effects of Oats Intake in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Nutrients* 2015; **7**: 10369-10387 [PMID: [26690472](#) DOI: [10.3390/nu7125536](#)]
- 26 **Slavin J**. Why whole grains are protective: biological mechanisms. *Proc Nutr Soc* 2003; **62**: 129-134 [PMID: [12740067](#) DOI: [10.1079/PNS2002221](#)]
- 27 **Newberne PM**, Suphakarn V. Nutrition and cancer: a review, with emphasis on the role of vitamins C and E and selenium. *Nutr Cancer* 1983; **5**: 107-119 [PMID: [6359073](#) DOI: [10.1080/01635588309513786](#)]
- 28 **Furman C**, Rundlöf AK, Larigauderie G, Jaye M, Bricca G, Copin C, Kandoussi AM, Fruchart JC, Arnér ES, Rouis M. Thioredoxin reductase 1 is upregulated in atherosclerotic plaques: specific induction of the promoter in human macrophages by oxidized low-density lipoproteins. *Free Radic Biol Med* 2004; **37**: 71-85 [PMID: [15183196](#) DOI: [10.1016/j.freeradbiomed.2004.04.016](#)]
- 29 **Huang Z**, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. *Antioxid Redox Signal* 2012; **16**: 705-743 [PMID: [21955027](#) DOI: [10.1089/ars.2011.4145](#)]
- 30 **Tinggi U**. Selenium: its role as antioxidant in human health. *Environ Health Prev Med* 2008; **13**: 102-108 [PMID: [19568888](#) DOI: [10.1007/s12199-007-0019-4](#)]
- 31 **Chen S**, Zhao X, Ran L, Wan J, Wang X, Qin Y, Shu F, Gao Y, Yuan L, Zhang Q, Mi M. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Dig Liver Dis* 2015; **47**: 226-232 [PMID: [25577300](#) DOI: [10.1016/j.dld.2014.11.015](#)]
- 32 **Tangvarasittichai S**. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World J Diabetes* 2015; **6**: 456-480 [PMID: [25897356](#) DOI: [10.4239/wjcd.v6.i3.456](#)]
- 33 **Belobrajdic DP**, Bird AR. The potential role of phytochemicals in wholegrain cereals for the prevention of type-2 diabetes. *Nutr J* 2013; **12**: 62 [PMID: [23679924](#) DOI: [10.1186/1475-2891-12-62](#)]
- 34 **Bozzetto L**, Annuzzi G, Pacini G, Costabile G, Vetrani C, Vitale M, Griffo E, Giacco A, De Natale C, Cocozza S, Della Pepa G, Tura A, Riccardi G, Rivellese AA. Polyphenol-rich diets improve glucose metabolism in people at high cardiometabolic risk: a controlled randomised intervention trial. *Diabetologia* 2015; **58**: 1551-1560 [PMID: [25906754](#) DOI: [10.1007/s00125-015-3592-x](#)]
- 35 **Clifton P**, Keogh J. Cholesterol-Lowering Effects of Plant Sterols in One Serve of Wholegrain Wheat Breakfast Cereal Biscuits-a Randomised Crossover Clinical Trial. *Foods* 2018; **7** [PMID: [29547511](#) DOI: [10.3390/foods7030039](#)]
- 36 **Salvin J**, Green H. Dietary fibre and satiety. *Nutr Bull* 2007; **32**: 32-42 [DOI: [10.1111/j.1467-3010.2007.00603.x](#)]
- 37 **Wanders AJ**, van den Borne JJ, de Graaf C, Hulshof T, Jonathan MC, Kristensen M, Mars M, Schols HA, Feskens EJ. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev* 2011; **12**: 724-739 [PMID: [21676152](#) DOI: [10.1111/j.1467-789X.2011.00895.x](#)]
- 38 **Lyly M**, Ohls N, Lähteenmäki L, Salmenkallio-Marttila M, Liukkonen KH, Karhunen L, Poutanen K. The effect of fibre amount, energy level and viscosity of beverages containing oat fibre supplement on perceived satiety. *Food Nutr Res* 2010; **54** [PMID: [20401343](#) DOI: [10.3402/fnr.v54i0.2149](#)]
- 39 **Sleeth ML**, Thompson EL, Ford HE, Zac-Varghese SE, Frost G. Free fatty acid receptor 2 and nutrient sensing: a proposed role for fibre, fermentable carbohydrates and short-chain fatty acids in appetite regulation. *Nutr Res Rev* 2010; **23**: 135-145 [PMID: [20482937](#) DOI: [10.1017/S0954422410000089](#)]
- 40 **Xi Y**, Xu PF. Diabetes and gut microbiota. *World J Diabetes* 2021; **12**: 1693-1703 [PMID: [34754371](#) DOI: [10.4239/wjcd.v12.i10.1693](#)]
- 41 **Bastos RMC**, Rangel ÉB. Gut microbiota-derived metabolites are novel targets for improving insulin resistance. *World J Diabetes* 2022; **13**: 65-69 [PMID: [35070060](#) DOI: [10.4239/wjcd.v13.i1.65](#)]
- 42 **Nilsson A**, Granfeldt Y, Ostman E, Preston T, Björck I. Effects of GI and content of indigestible carbohydrates of cereal-based evening meals on glucose tolerance at a subsequent standardised breakfast. *Eur J Clin Nutr* 2006; **60**: 1092-1099 [PMID: [16523203](#) DOI: [10.1038/sj.ejcn.1602423](#)]
- 43 **Sánchez D**, Miguel M, Aleixandre A. Dietary fiber, gut peptides, and adipocytokines. *J Med Food* 2012; **15**: 223-230 [PMID: [22181071](#) DOI: [10.1089/jmf.2011.0072](#)]
- 44 **McRorie JW Jr**. Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 1: What to Look for and How to Recommend an Effective Fiber Therapy. *Nutr Today* 2015; **50**: 82-89 [PMID: [25972618](#) DOI: [10.1097/NT.0000000000000082](#)]
- 45 **Bodnaruc AM**, Prud'homme D, Blanchet R, Giroux I. Nutritional modulation of endogenous glucagon-like peptide-1 secretion: a review. *Nutr Metab (Lond)* 2016; **13**: 92 [PMID: [27990172](#) DOI: [10.1186/s12986-016-0153-3](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

