UNIVERSITI PUTRA MALAYSIA

EFFECT OF MULTISTRAIN PROBIOTIC SUPPLEMENTATION IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

SOMAYYEH FIROUZI

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By

SOMAYYEH FIROUZI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

June 2015

DEDICATION

This thesis work is dedicated to my husband, Dr. Aidin Sadeghilar, who has been a constant source of support and encouragement during the challenges of graduation and life. I am truly thankful for having you in my life.

This work is also dedicated to my family, parents, sisters and my brother who love me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

EFFECT OF MULTISTRAIN PROBIOTIC SUPPLEMENTATION IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

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June 2015

Chairman : Barakatun Nisak Mohd Yusof, PhD
Faculty : Medicine and Health Sciences

Probiotics is reported as one of the option to achieve optimum glycemic control. While findings in animal models were convincing, evidences from human clinical trial are still controversial. To address this research gap, the double blind randomized controlled trial was conducted to investigate the effect of 12 weeks supplementation with multistrain probiotics in individuals with type 2 diabetes.

A total of 136 participants with Type 2 Diabetes and aged 30-70 (mean Body Mass index (BMI): 29.2 kg/m^2 in Probiotic Group and 29.3 kg/m^2 in Placebo Group; Mean Glycated Hemoglobin (HbA1c): 7.6% in Probiotic Group and 7.5% in Placebo Group) participated in the study. Participants were asked to maintain their dietary intake and physical activity levels throughout the study. Participants were randomly assigned to receive daily dose of 6×10^{10} multistrain probiotic supplement.

Changes in glycemic control variables, anthropometric measures, BMI, fasting lipid, renal profile, liver function, blood pressure, and high sensitivity C-reactive protein were measured at baseline, week 6 and 12 of the study. Adherence was assessed by calculating the number of remaining sachets. In a sub-samples (n=40), their stool were collected to determine the Colony Forming Units (CFUs) of *Lactobacillus* and *Bifidobacterium* using the plate count method. Sensitivity analyses namely Intention to Treat (ITT) and Per Protocol (PP) analyses were performed using General Linear Model Analysis of Variance. The ITT analysis conducted on the full set of data while the PP analysis was performed on those who have completed the study with more than 85% adherence.

Baseline characteristics of the participants were comparable in both groups except for the liver status. The attrition rate was 20.6%. Participants maintained their dietary intake and physical activity throughout the study period. HbA1c decreased 0.2% in Probiotic Group while remains unchanged in Placebo Group. These differences were not significant between Probiotics and Placebo Groups in ITT analyses but in PP analysis, the differences were significant (p=0.017). Fasting insulin increased 0.8 µU/mL in the Placebo Group and decreased 1.6 µU/mL in the Probiotic Group. These changes were significant in both the ITT (p=0.020) and PP (p=0.016) analyses. Serum

urea levels reduced by 0.22 mmol/L in the Probiotic Group while it increased by 0.21 mmol/L in Placebo Group and the differences were significant in ITT analysis (p=0.018). Other outcomes did not change significantly between groups. In a sub-samples, the *Lactobacillus* (from 6.4×10^6 to 1.3×10^7 CFU/g; p=0.05) and the *Bifidobacterium* (from 3.4×10^6 to 1.3×10^7 CFU/g; p=0.02) species were significantly increased in Probiotics Groups as compared to Placebo Group in ITT

Multistrain probiotics supplementation for a 12-week period influenced glycemic control variables and diabetes-related outcomes in individuals with Type 2 Diabetes. It was effective to improve the fasting insulin and urea levels as well. The improvements in HbA1c levels were also greater among those participants who have completed the trial with good adherence.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN SUPLEMEN PROBIOTIK MULTISTRAIN DALAM KALANGAN INDIVIDU YANG MEMPUNYAI DIABETES JENIS 2

Oleh

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Probiotik dilaporkan adalah sebagai salah satu pilihan dalam mencapai kawalan glisemik yang optimum. Walaupun hasil kajian dalam model haiwan amat memberangsangkan, bukti daripada kajian klinikal manusia masih kontroversi. Untuk menangani jurang ini, kajian rawak terkawal gelap ganda telah dijalankan untuk mengkaji kesan pemberian suplemen probiotik multistrain selama 12 minggu dalam kalangan individu yang mempunyai diabetes jenis 2.

Seramai 136 peserta dengan diabetes Jenis 2 dan berumur berumur 30-70 tahun (min indeks jisim tubuh (IJT): 29.2 kg/m^2 dalam Probiotik Kumpulan dan 29.3 kg/m^2 di Placebo Kumpulan; Min Glycated Hemoglobin (HbA1c): 7.6% pada Probiotik Kumpulan dan 7.5% pada Placebo Kumpulan) telah menyertai kajian ini. Peserta telah diminta untuk mengekalkan pengambilan makanan dan aktiviti fizikal sepanjang kajian. Peserta telah di aturkan secara rawak untuk menyertai Kumpulan Probiotik (n=68) atau Plasebo (n=68). Peserta perlu mengambil paket yang mengandungi probiotik atau plasebo dos harian 6 × 1010 multistrain makanan tambahan probiotik.

Perubahan dalam variabel kawalan glisemik, ukuran antropometri, IJT, aras berpuasa lipid, profil renal, fungsi liver, tekanan darah, dan protein C-reaktif tinggi sensitiviti telah diukur pada aras asas, minggu 6 dan 12 kajian. Kepatuhan telah dinilai dengan mengira jumlah paket yang masih berbaki. Dalam sub-sampel peserta (n=40), najis mereka telah dikumpulkan bagi menentukan *Colony Forming Units (CFUs)* ke atas *Lactobacillus* dan *Bifidobacterium* menggunakan kaedah kiraan plat. Analisis sensitiviti iaitu *Intention to Treat (ITT)* dan *Per Protocol (PP)* analisis telah dilakukan menggunakan *General Linear Model Analysis of Variance.* Analisis ITT telah dijalankan ke atas set data yang lengkap manakala analisis PP telah dijalankan ke atas peserta yang telah menamatkan kajian dengan mencapai tahap kepatuhan yang tinggi melebihi 85%.

HbA1c menurun sebanyak 0.2% dalam Kumpulan Probiotik manakala kekal tidak berubah dalam Kumpulan Plasebo. Perubahan ini adalah tidak signikan antara kumpulan dalam analisa ITT tetapi dalam analisa PP, perubahan ini adalah signikan (p=0.017). Insulin berpuasa meningkat sebanyak 0.8 µU/mL dalam Kumpulan Plasebo dan menurun sebanyak 1.6 µU/mL dalam Kumpulan Probiotik. Perubahan ini adalah

signikan bagi kedua-dua analisa ITT (p=0.020) dan PP (p=0.016). Aras serum urea menurun sebanyak 0.22 mmol/L dalam Kumpulan Probiotik manakala ia meningkat sebanyak 0.21 mmol/L dalam Kumpulan Plasebo dan perbezaan ini adalah signifikan dalam analisa ITT (p=0.018). Hasil lain tidak berubah secara signifikan antara kumpulan. Dalam sub-sampel analisa, spesies *Lactobacillus* (dari 6.4×10^6 kepada 1.3×10^7 CFU/g; p=0.05) dan *Bifidobacterium (*dari 3.4×10^6 kepada 1.3×10^7 CFU/g; p=0.02) meningkat secara signifikan dalam Kumpulan Probiotik berbanding Plasebo menggunakan analisa ITT.

Suplemen probiotik multistrain selama 12 minggu mempengaruhi variabel kawalan glisemik dan hasil berkaitan diabetes dalam kalangan individu dengan diabetes jenis 2. Ia adalah efektif memperbaiki aras insulin berpuasa dan urea. Penambahbaikan dalam aras HbA1c adalah lebih baik bagi peserta yang telah menamatkan kajian dengan kadar kepatuhan yang baik.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

3DDR	3-Day Diet Record
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
bp	base per
B:F ratio	*Bacteroidetes* to *Firmicutes* ratio
CFU	Colony Forming Unit
CONSORT	Consolidated Standards of Reporting Trials
CI	Confidence Interval
DBP	Diastolic Blood Pressure
EASD/ADA	American Diabetes Association and the European Association for the Study of Diabetes
FBS	Fasting Blood Glucose
GLM ANOVA	General Linear Model Analysis of Variance
GFR	Glomerular Filtration Rate
GLP-1	Glucagon Like Peptide 1
GLP-2	Glucagon Like Peptide 2
HbA1c	Hemoglobin A1c
HDL-C	High Density Lipoprotein cholesterol
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HS CRP	High Sensitivity C- Reactive Protein
IL	Interleukin
IPAQ	International Physical Activity Questionnaire
ITT	Intention To Treat
LDL-C	Low Density Lipoprotein Cholestrol
LLD	Lipid Lowering Drugs
MNT	Medical Nutrition Therapy
MRS	de Man, Rogosa and Sharpe
NMRR	National Medical Research Register
NHMS III	Third National Health and Morbidity Survey
OAD	Oral Anti-Diabetic agents
OW/OB	Overweight Obese
PP	Per Protocol
QUICKI	Quantitative Insulin Sensitivity Check Index
SBP	Systolic Blood Pressure
SE	Standard Error
DBP	Diastolic Blood Pressure
TC	Total Cholesterol
TG	Triglycerides
TNFα	Tumor Necrosis Factor Alpha
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
WC	Waist Circumference

CHAPTER 1

INTRODUCTION

Type 2 Diabetes Mellitus is the most common form of diabetes, a metabolic disorder characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both (Das & Elbein, 2006). The prevalence has been increased daramatically worldwide in Asian countries (Ramachandran, Wan Ma, & Snehalatha, 2010a). Type 2 Diabetes is a multifactorial disease with wide range of risk factors including genetic, lifestyle, obesity, family history and ethnicities. Management of Type 2 Diabetes involves multi-dimensional approach including various types of glycemic-targeted medications and lifestyle modifications (Fallucca, Porrata, Fallucca, & Pianesi, 2014; Rawal et al., 2012). While multi appproaches are available in managing Type 2 Diabetes, poor glycemic control is still highlyprevalent (Ramachandran et al., 2010). Hence, there is a need for any complementary approached that help to manage Type 2 Diabetes.

Recent studies have revealed a link between gut microbiota and diabetes (Cani et al., 2009; Chen, Wang, & Li, 2011; Naito et al., 2011). Larsen et al. (2010) showed that gut microbiota in diabetic indiviudals differed significantly in terms of type and count of microorganism as compared with healthy counterparts. Indeed, the level of glucose tolerance was associated with specific microbiota found in healthy individuals. Gut microbiota was found to be strongly associated with numerous major physiological functions especially the pro-inflammatory processes (Musso, Gambino, & Cassader, 2010). It is worth to mention that Type 2 Diabetes is partly due to inflammation (Fallucca et al., 2014; Membrez et al., 2008; Tremaroli & Bäckhed, 2012). From the above studies, it is hypothesized that manipulation of gut microbiota have the potential to favorably impact glycemic control (Burcelin, Serino, Chabo, Blasco-Baque, & Amar, 2011; Delzenne, Neyrinck, & Cani, 2011).

In view of this, probiotics have been introduced as a recent dietary intervention which is able to modulate gut microbiota (Musso et al., 2010). Probiotics are viable microorganisms that in certain dosage confer health benefits to the host through many different ways. These live microorganisms have the ability to alter type and count of gut microbiota (Lye, Kuan, Ewe, Fung, & Liong, 2009). Alteration of gut microbiota will affect physiological functions of the gut and have the potential to improve some diseases. In recent years, the benefits of probiotics have undergone increasing scientific scrutiny. While the benefits of probiotics on gut health have been confirmed (Rowland et al., 2010; Sanmugapriya, Jayasimhan, Yap, Roest, Rajandram, & Chin, 2013; Song et al., 2010), its usage for the management of chronic diseases is still under investigation (Asemi, Zare, Shakeri, Sabihi, & Esmaillzadeh, 2013; Karimi, Jamaluddin, & Parvaneh, 2013; Sadrzadeh-Yeganeh et al., 2010).

As discussed above, gut microbiota is related to diabetes and glucose intolerance (Larsen et al., 2010; Musso et al., 2010). Thus, it is possible that probiotics will help managing diabetes by manipulating gut microbiota. Animal studies and human trials have shown that probiotics supplementation has had a positive impact on preventing the onset of diabetes (Calcinaro et al., 2005; Yadav, Jain, & Sinha, 2007; Yamano et

al., 2006) and helping to manage the glycemic control in individuals with Type 2 Diabetes who are on treatment with Oral Anti Diabetic agents (OAD) (Andersson et al., 2010; Chen et al., 2011; Ejtahed, Mohtadi Nia, Homayouni Rad, Niafar, Asghari Jafarabadi, & Mofid, 2011; Naito et al., 2011). However, finding were still controversial in which probiotics did not affect glycemic control among obese Danish adolescents (Gobel, Larsen, Jakobsen, Molgaard, & Michaelsen, 2012) and overweight and obese Australian adults (Ivey et al., 2014). In in dividuals with Type 2 Diabetes, improvements were noted among Iranian type 2 diabetics (Ejtahed, et al, 2011a) and in a mix group of healthy and diabetics in Denmark (Andreasen et al., 2010). On the other hand, two studies in Iranian Type 2 Diabetic individuals did not report any significant improvements on glycemic control (Asemi, Zare, Shakeri, Sabihi, & Esmaillzadeh, 2013; Mazloom, Yousefinejad, & Dabbaghmanesh, 2013).

Studies have shown that the positive effects in glycemic control may be achieved through improvements in inflammatory status (Chen et al., 2011; Naito et al., 2011), empowering antioxidant status (Ejtahed et al., 2012), or changes in harvest of energy (Turnbaugh et al., 2009). However, data on human studies is still limited and controversial. Probiotics have the potential as an adjuvant therapy for management of glycemic control but this hypothesis need to be further examined in the context of Type 2 Diabetes Mellitus.

Type 2 Diabetes is not only characterized by high blood glucose levels but also manifested by a cluster of co-morbidities which include obesity, dyslipidemia, hypertension, chronic kidney and liver disease. Studies have shown that probiotics have had beneficial impact on the latter conditions as well (Hatakka, Mutanen, Holma, Saxelin, & Korpela, 2008; Lye et al., 2009). Studies have shown promising results in improving anthropometic measures (Caesar, Fåk, & Bäckhed, 2010; Luoto, Kalliomäki, Laitinen, & Isolauri, 2010), lipid profile (Ejtahed, Mohtadi Nia, Homayouni Rad, Niafar, Asghari Jafarabadi, Mofid, 2011b; Rajkumar et al., 2014), blood pressure (Lye, Kuan, Ewe, Fung, & Liong, 2009), renal profile (Alatriste, Arronte, Espinosa, & Cuevas, 2014) or liver function (Ma, Hua, & Li, 2008). Hence, cumulative effect of probiotics on glycemic control and other diabetes related co-morbidities may augment the beneficial impact of probiotic supplementation for those with Type 2 Diabetes Mellitus. This introduces an added advantage for using probiotics as an adjuvant therapy for Type 2 Diabetes as it has the potential to beneficially affect glycemic control together with other diabetes-related comorbidities.

Problem Statement

As mentioned before, the prevalence of Type 2 Diabetes Mellitus is increasing worldwide. In Malaysia, the prevalence of Type 2 Diabetes was reported to be 22.6% in 2013 (Wan Nazaimoon et al., 2013). Despite intensive efforts to control diabetes, many diabetics have found a steady rise in plasma glucose level that occurs over time. As such, it is no surprise that poor blood glucose control is highly prevalent among individuals with Type 2 Diabetes. Majority of the people with diabetes in Malaysia have not achieved satisfactory control over their glycemic variables. They presented with mean HbA1c of 8.6±2.1% and only 22% of them achieved the target goal of <7%. Microvascular and macrovascular complications were reported in 75% and 29% people with diabetes respectively. (Mafauzy, Hussein, & Chan, 2011). Poor adherence to the diet and physical activity has been generally acknowledged among individuals with Type 2 Diabetes (Delamater, 2006) especially in Malaysia (Mafauzy, Hussein, & Chan,

2011). In general, evidence is mounting that dietary advice and medical management alone may not be enough to achieve favorable glycemic control, prompting interest in other therapeutic strategies particularly the functional food (Fallucca et al., 2014).

The importance of the interaction between gut microbiota and the host physiological functions is increasingly being recognized (Tremaroli & Bäckhed, 2012). The use of probiotics to modulate gut microbiota with favourable impacts on physiological conditions has received much attention in recent years (Burcelin et al., 2011; Fallucca et al., 2014; Leber et al., 2012). Animal studies have proved that the modulation of gut microbiota by using probiotics led to improvements in glucose homeostasis (An et al., 2011; Chen et al., 2011; Naito et al., 2011); this was also noted in a few human trials (Andreasen et al., 2010; Ejtahed et al., 2011a; Laitinen et al., 2009). Several clinical trials have been conducted to examine the effects of probiotics in individuals with Type 2 Diabetes (Andreasen et al., 2010; Asemi et al., 2013; Ejtahed et al., 2011a; Mazloom et al., 2013). However, data regarding the impact of probiotics in individuals with Type 2 Diabetes is still limited due to small sample size of earlier trials and the inconsistency of the results. Besides, the results of other studies may not be extrapolated to apply to Malaysian population due to the differences in genetic, food consumption pattern, environmental and cultural differences.

The structure of gut microbiota is partly influenced by the dietary intake especially fiber (Slavin, 2013). However, individuals with Type 2 Diabetes in Malaysia reported to only consume about 11 gram of fiber in a day (Barakatun-Nisak, Talib, Norimah, & Gilbertson, 2010) which was far below the recommended >25g per day (Malaysian Dietitians' Association, 2013). Additionally, traditional probiotic products such as yoghurt are not a routine part of a diet among Malaysians. Thus, it can be hypothesized that Malaysians with Type 2 Diabetes do not have enough probiotics in their gut. Therefore, probiotic supplementation may be beneficial for this population.

Research Question

Issues related to the use of probiotics to improve glycemic control have led to the following research questions:

1. Does administration of probiotics to individuals with diet controlled Type 2 Diabetes or people with orally treated Type 2 Diabetes lead to improvements in fasting blood glucose, insulin concentration, glycated hemoglobin, and insulin resistance?

2. Does the administration of probiotics to individuals with diet controlled Type 2 Diabetes or people with orally treated Type 2 Diabetes lead to changes in gastrointestinal microbiota?

Significance of the Study

The finding of this study provided fundamental data on the quantities of *Lactobacillus* and *Bifidobacterium* presented in the gut of Malaysians who have Type 2 Diabetes; this information were not available at this time. Additionally, the study provides information whether by having probiotic supplement the concentrations of *Lactobacillus* and *Bifidobacterium* will be changed. This serves as a reference for the

baseline gut status of individuals with Type 2 Diabetes in Malaysia useful for future research.

This study offers some insights into the role of probiotics to impact glycemic control in individuals with Type 2 Diabetes. The outcomes of this study provided data regarding the impact of probiotics on other diabetes related complication including obesity, dyslipidemia, liver function, renal profile, blood pressure, and inflammatory status.

This is pertinent in the present context as individuals with Type 2 Diabetes in Malaysia have been documented to have poor glycemic control and fall short of their target. Therefore, the study will benefit this group by helping them to improve glycemic control and other diabetes related complications. Health professional may recommend this dietary approach to enhance the impact of the other approaches commonly used in management of diabetes. In this regards, a more specific probiotic supplement which fits best for their target group can be developed.

Objectives

To investigate the effect of probiotic supplementation in individuals with Type 2 Diabetes.

Specific Objectives:

1. To compare the effects of Probiotics versus Placebo on glycemic control variables including fasting blood glucose, Hemoglobin A1c, fasting insulin levels, insulin resistance and insulin sensitivity in individuals with Type 2 Diabetes in week 6 and week 12 of supplementation.

2. To compare the effects of Probiotics versus Placebo on anthropometry measurements, lipid and renal profile, liver function, blood pressure, and inflammatory marker in individuals with Type 2 Diabetes in week 6 and week 12 of supplementation.

3. To compare the effects of Probiotics versus Placebo on the quantity of *Lactobacillus* and *Bifidobacterium* in stool sample at baseline and week 12 of supplementation.

Hypothesis

The administration of probiotics to people with Type 2 Diabetes will lead to improvements in:

- Fasting blood glucose and insulin concentration, HbA1c, and insulin resistance
- Anthropometry measurements and BMI
- Lipid profile
- Blood pressure
- Inflammatory marker
- Renal profile and liver function
- Quantities of *Lactobacillus* and *Bifidobacterium* in stool sample

Conceptual Framework

This study aimed to show that probiotic supplementation has beneficial effects on the gut microbiota. Improvements in gut microbiota lead to improvements in glycemic control, anthropometry status, lipid and renal profile and liver function, inflammatory status and blood pressure (Figure 1.1).

Individuals with type 2 diabetes are usually on life style modifications and a broad range of medications makes it difficult to find a homogenous sample of them being under same treatment modalities. These variations may enter bias into the study. For example, diet, physical activity and medications used by the participants serve as a confounding factor and should be controlled throughout the study.

Diet plays an important role to improve either gut or diabetes-related outcomes. Physical activity on the other hand plays a role in the control of diabetes-related variables. Diet was controlled and managed by providing nutrition booklet for the participants. Participants were asked not to change the levels of their physical activity during the course of the study in order to adjust the confounding effect of physical activity. The medications affect glycemic control and other diabetes-related outcomes. Confounding effect of medications was adjusted by recruiting participants who were taking stabilized dose of medication. Indeed, these three variables were adjusted for these medications in case there were significant differences in the prevalence of taking medications between groups at baseline.

In order to assess the successful passage of the supplement from gastrointestinal tract, the quantities of *Lactobacillus* and *Bifidobacterium* were measured before and after intervention.

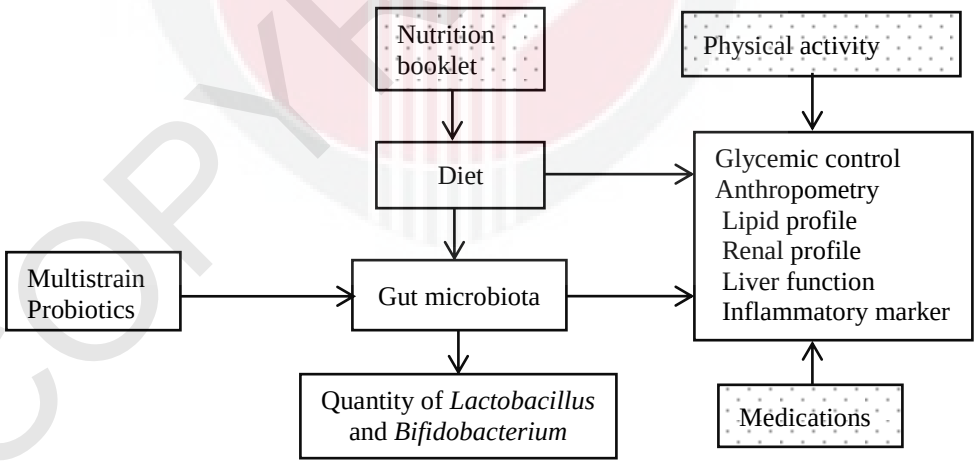

Figure 1.1. Operational Framework

The pattern boxes demonstrating the confounding factors which have been adjusted in this study

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