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MOLECULAR MODULATION OF MEDICAL NUTRITION THERAPY IN OBESE PATIENTS WITH TYPE 2 DIABETES MELLITUS

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By

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MOLECULAR MODULATION OF MEDICAL NUTRITION THERAPY IN OBESE PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Chair: Associate Professor Hoo Fan Kee, MD, MRCPS
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The number of adults with diabetes has reached a global prevalence of approximately 9.3%, 463 million in 2019. According to the International Diabetes Federation, this prevalence is projected to rise sharply by 51%, affecting 700 million adults worldwide by 2045. Dysregulation of peroxisome proliferator-activated receptors (PPARs) and its' coactivator *PPAR gamma co-activator-1-alpha* (*PPARGC1A*) in fatty acid oxidation (FAO) and increased inflammation are among the main factors leading to the pathogenesis of type 2 diabetes mellitus (T2DM), obesity, cardiovascular disease (CVD) and metabolic syndrome. Medical nutrition therapy (MNT) has become one of the primary clinical guidelines in diabetes management, and sustained weight loss via MNT of merely 3% to 5% has the ability to produce clinical health improvements such as reductions in CVD risk factors and glycaemic control. We hypothesised that weight loss would modulate molecular changes that underlie favourable clinical health improvement.

The obese patients with T2DM were randomised to either energy-restricted isocaloric MNT or conventional dietetic therapy (CDT) arms for endpoint interventions. Clinical phenotypes, the PPARs pathway target genes expressions and deoxyribonucleic acid (DNA) methylation promoter region of *PPARGC1A* were measured at baseline and endpoint intervention from peripheral blood mononuclear cells (PBMC). The lean non-diabetic participants were recruited as baseline characteristics of the PPARs target genes. Genotyping of single nucleotide polymorphism (SNP) of Pro12Ala and Gly482Ser from the *PPAR gamma* (*PPARG*) and *PPARGC1A* as well as Leu162Val polymorphism in *PPAR alpha* (*PPARA*) were conducted from PBMC of the T2DM with obesity patients. Genotyping of SNPs serves to assess the association of SNPs with clinical phenotypes. The PBMC was used as a surrogate for metabolic tissues, and bariatric patients were recruited to validate study findings by elucidating whether transcriptional

regulation of *PPARs* pathway in PBMC was associated with skeletal muscle, visceral fat (VF) and subcutaneous fat (SF).

Our results showed that, firstly, the MNT arm demonstrated a significant reduction in weight and other clinical phenotypes associated with the improvement of CVD risk factors and glycaemic control ($p<0.05$), irrespective of SNPs variants; whereas the CDT arm did not demonstrate significant changes in pre-and post-intervention except diastolic pressure reduction. However, T2DM patients in the CDT arm with 12Ala carriers displayed a significant reduction in body composition and glycaemic level, indicating the predisposition effect of SNPs on conventional dietary responses ($p<0.05$), but there is no association found between MNT arm and SNPs ($p>0.05$). The MNT arm had achieved over 80% adherence to the dietary regime, a substantial improvement compared to previously reported 16.4% adherence. Secondly, The FAO and anti-inflammatory pathway's gene expression of T2DM obese patients were down-regulated than lean non-T2DM. However, at the endpoint, these genes were up-regulated in the MNT arm and significantly associated with the improvement of clinical phenotypes ($p<0.05$). Thirdly, the transcriptional upregulation of PPARs target gene was inversely associated with DNA methylation in the *PPARGC1A* promoter region ($p<0.05$) in both arms, but no transcriptional association was associated with the SNPs ($p>0.05$) in both arms. Fourthly, both the PBMC's PPARs pathway transcriptional regulation and DNA methylation profile in promoter regions were well associated with the skeletal muscle of the bariatric patients ($p<0.05$), indicating the feasibility of PBMC as a prospective diagnostic tool, at least as a surrogate for skeletal muscle.

In conclusion, the reduction of DNA methylation profile in *PPARGC1A* promoter region up-regulates gene expression of PPARs target gene in obese T2DM at pre-and post-intervention, contributing to clinical improvements. Our study indicates that epigenetic demonstrates superiority over genetic predisposition. Since epigenetic modification is inheritable but reversible, current discoveries provide mechanistic insight to improve diagnosis, therapy and prevention to T2DM, obesity and CVD management.

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

MODULASI MOLEKUL KE ATAS TERAPI NUTRISI PERUBATAN DALAM KALANGAN PESAKIT OBES YANG MENGHIDAP DIABETES MELLITUS JENIS 2

Oleh

TAY SOOK HUI

Mei 2021

Pengerusi: Profesor Madya Hoo Fan Kee, MD, MRCPS
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Jumlah orang dewasa dengan diabetes telah mencapai prevalensi global sekitar 9.3%, 463 juta pada tahun 2019. Menurut Persekutuan Diabetes Antarabangsa, prevalensi ini diproyeksikan meningkat tajam sebanyak 51%, yang mempengaruhi 700 juta orang dewasa di seluruh dunia pada tahun 2045. Disregulasi peroksisom reseptor yang diaktifkan proliferator (PPARs) dan 'koaktivator *PPAR gamma co-activator-1-alpha* (*PPARGC1A*) dalam pengoksidaan asid lemak (FAO) dan peningkatan keradangan adalah antara faktor utama yang menyebabkan patogenesis diabetes mellitus jenis 2 (T2DM), kegemukan, penyakit kardiovaskular (CVD) dan sindrom metabolik. Terapi pemakanan perubatan (MNT) telah menjadi salah satu garis panduan klinikal utama dalam pengurusan diabetes dan penurunan berat badan yang berterusan melalui MNT hanya 3% hingga 5% mempunyai kemampuan untuk menghasilkan peningkatan kesihatan klinikal seperti pengurangan faktor risiko CVD dan kawalan glisemik.

Peserta obes dengan T2DM secara rawak sama ada dengan MNT isokalori terhad tenaga atau terapi terapi diet konvensional (CDT) untuk intervensi titik akhir. Fenotip klinikal, ekspresi gen sasaran PPARs jalur dan wilayah penggerak metilasi DNA *PPARGC1A* diukur pada intervensi awal dan titik akhir dari sel mononuklear darah periferal (PBMC). Peserta langsing tanpa diabetes direkrut sebagai ciri asas gen sasaran PPAR. Genotip polimorfisme nukleotida tunggal (SNP) Pro12Ala dan Gly482Ser dari *PPAR gamma* (*PPARG*) dan *PPARGC1A* serta polimorfisme Leu162Val dalam *PPAR alpha* (*PPARA*) dilakukan dari PBMC T2DM dengan peserta obes. Genotip SNP berfungsi untuk menilai perkaitan SNP dengan fenotip klinikal. Untuk mengesahkan penemuan kajian semasa di PBMC sebagai pengganti untuk tisu metabolik, pesakit bariatrik direkrut untuk menjelaskan sama ada

peraturan transkripsi jalur PPAR di PBMC dikaitkan dengan otot rangka, lemak viseral (VF) dan lemak subkutan (SF).

Hasil kajian kami menunjukkan bahawa, pertama, kumpulan MNT menunjukkan penurunan berat badan dan fenotip klinikal lain yang berkaitan dengan peningkatan faktor risiko CVD dan kawalan glisemik ($p<0,05$), tanpa mengira varian SNP; sedangkan kumpulan CDT tidak menunjukkan perubahan yang signifikan dalam intervensi sebelum dan pasca kecuali pengurangan tekanan diastolik. Walau bagaimanapun, pesakit T2DM di kumpulan CDT dengan pembawa 12Ala menunjukkan penurunan yang ketara dalam komposisi badan dan tahap glisemik, menunjukkan kesan predisposisi SNP pada tindak balas diet konvensional ($p<0.05$) tetapi tidak ada hubungan yang dijumpai antara kumpulan MNT dan SNP ($p>0.05$). Kumpulan MNT telah mencapai kepatuhan lebih dari 80% terhadap rejim diet, peningkatan yang ketara dibandingkan dengan kepatuhan yang dilaporkan sebelumnya sebanyak 16.4%. Kedua, ekspresi gen FAO dan kaedah anti-radang pesakit T2DM yang gemuk diatur lebih rendah daripada tanpa T2DM tanpa lemak. Walau bagaimanapun, pada titik akhir, gen-gen ini diatur di lengan MNT dan dikaitkan secara signifikan dengan peningkatan fenotip klinikal ($p<0,05$). Ketiga, pengaturan transkripsional gen sasaran PPAR dikaitkan secara terbalik dengan metilasi DNA di kawasan pendorong *PPARGC1A* ($p<0.05$) di kedua-dua lengan; tetapi tidak ada hubungan transkrip yang dikaitkan dengan SNP ($p>0.05$) di kedua-dua lengan. Keempat, kedua-dua peraturan transkripsional jalur PPAR PBMC dan profil metilasi DNA di kawasan promoter berkaitan dengan otot rangka pesakit bariatrik ($p<0.05$), menunjukkan kemungkinan PBMC sebagai alat diagnostik prospektif, sekurang-kurangnya sebagai pengganti otot rangka.

Kesimpulannya, pengurangan profil metilasi DNA di wilayah promoter *PPARGC1A,* mengatur ekspresi gen sasaran *PPAR* pada T2DM obes pada pra-dan pasca intervensi, yang menyumbang kepada kemajuan klinikal. Kajian kami menunjukkan bahawa epigenetik mengatasi kecenderungan genetik. Oleh kerana pengubahsuaian epigenetik dapat diwariskan tetapi dapat diterbalikkan, penemuan terkini memberikan wawasan mekanistik untuk meningkatkan diagnosis, terapi dan pencegahan terhadap T2DM, kegemukan dan pengurusan CVD.

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This thesis was submitted to the Senate of Universiti Putra Malaysia, and the University of Nottingham have been accepted as fulfilment of the requirement for the Degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

ACAA2	Acetyl-Coenzyme A acyltransferase 2
ADA	America Diabetes Association
AdipoR2	Adiponectin receptor 2
AdjR^2	Adjusted R^2
AGI	Alpha-glucosidase inhibitor
AHEAD	Action for Health in Diabetes
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APA	American Psychological Association
ATP	Adenosine triphosphate
AST	Aspartate aminotransferase
BF	Body Fat
BIA	Bioelectrical impendence analysis
BMI	Body mass index
BMR	Basal metabolic rate
bp	Base pair
cDNA	Complementary deoxyribonucleic acid
CDA	Canadian Diabetes Association
CDT	Conventional dietetic therapy
CI	Confidence interval
cm	Centimetre(s)
CONSORT	Consolidated standards of reporting trials

CPG	Clinical Practice Guideline
CPT1A	Carnitine palmitoyltransferase 1 alpha
Cq	Quantification cycle
CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
dL	Decilitre(s)
DNA	Deoxyribonucleic acid
DNase	Deoxyribonuclease
DPP-4i	Dipeptidyl peptidase-4 inhibitor
E	Efficiency
EASD	European association for the study of diabetes
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EI	Energy intake
ES	Effect size
FA	Fatty acid(s)
FAO	Fatty acid oxidation
FPG	Fasting plasma glucose
g	Gram(s)
GAPDH	Glyceraldehyde3-phosphate dehydrogenase
GC	Guanine-cytosine
GGT	Gamma-glutamyl transferase
GLM	Generalized Linear Model
GLP-1	Glucagon-like peptide 1
GOI	Gene of interest

GWAS	Genome-wide association studies
h	Hour(s)
H_0	Null hypothesis
H_a	Alternative hypothesis
HbA1c	Glycated haemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HIV+	Human immunodeficiency virus positive
hs-CRP	High-sensitivity C-reactive protein
IMO	Institute of Medicine of The National Academics
IPAQ-SF	International physical activity questionnaire-short format
kcal	Kilocalorie(s)
kg	Kilogram(s)
km	Kilometre(s)
L	Litre(s)
LDL-C	Low density lipoprotein cholesterol
Log_{10}	Logarithms base 10
m	Metre(s)
MD	Mean difference
min	Minute(s)
min/wk	Minutes per week
MIQE	Minimum Information for Publication of Quantitative Real-Time PCR Experiments
mg	Milligram(s)
mg/dL	Milligrams per decilitre
mM	millimolar
mm Hg	Millimetres of mercury

ml	Millilitre(s)
MNT	Medical nutrition therapy
mmol	Millimole(s)
mmol/L	Millimoles per litre
mmol/mol	Millimoles per mole
mol	Mole(s)
MR	Meal replacement
mRNA	Messenger ribonucleic acid(s)
MRT	Meal replacement therapy
MSE	Mean of square error
MUFA	Monounsaturated fatty acids
N/A	Not available
ng/μl	Nano grams per microlitre
NICE	National Institute for Health and Care Excellence
NS	Non-significant
NTC	No template controls
OAD	Oral anti-diabetic drug(s)
OGTT	Oral glucose tolerance test
PATh	Patient algorithm for nutrition therapy
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PDC	Pyruvate dehydrogenase complex
PDK4	Pyruvate dehydrogenase kinase 4
PGK1	Phosphoglycerate kinase 1

PPAR	Peroxisome proliferator-activated receptor(s)
PPARGC1A	Peroxisome proliferator-activated receptor gamma co-activator 1 alpha
PPARA	Peroxisome proliferator-activated receptor alpha
PPARD	Peroxisome proliferator-activated receptor delta
PPARG	Peroxisome proliferator-activated receptor gamma
PPi	Pyrophosphate
PPREs	Peroxisome proliferator response elements
PUFA	Polyunsaturated fatty acids
qPCR	Quantitative real-time polymerase chain reaction
RCT	Randomized controlled trial
REF	Reference gene
rmp	Revolution per minute
RMR	Resting metabolic rate
RNA	Ribonucleic acid
RNase	Ribonucleases
RXR	9-*cis*-retinoic acid X receptor
s	Second(s)
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of mean
SF	Subcutaneous fat
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
SLC25A20	Solute carrier family 25 (carnitine/acylcarnitine translocase), member 20
SNP	Single nucleotide polymorphism(s)
SU	Sulphonylureas

T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TC/HDL-C	Total cholesterol/high density lipoprotein cholesterol
TG	Triglycerides
TZD	Thiazolidinediones
UK	United Kingdom
US	United States
USA	United States of America
VF	Visceral fat
VLDL	Very low density lipoprotein cholesterol
WHO	World Health Organisation
μl	Microlitre(s)
°C	Celsius
%	percentage(s)
α	Alpha
β	Beta
ω3	Omega 3
ω6	Omega 6
ω9	Omega 9

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Scope of Study

T2DM is one of the fastest-growing lifestyle diseases globally, and the majority is attributed to Asian countries such as Malaysia (Hussein *et al.*, 2013; Zheng, Ley and Hu, 2018). Weight loss of 3-5% from lifestyle intervention, particularly with MNT, is the cornerstone of treatment for optimal glucose control and CVD risk factors for diabetic patients insistently endorsed by the American Diabetes Association and Clinical Practice Guideline (CPG) for T2DM Management in Malaysia (Jensen *et al.*, 2014; Clinical Practice Guidelines Development Group, 2015; Fox *et al.*, 2015; American Diabetes Association, 2019a, 2019b). T2DM and obesity are multifactorial disorders encompassing the interaction between genetic and environmental elements.

The primary outcome of the study was to attain at least 3% of body weight reduction at the trial endpoint and to find its association with the glycaemic control [glycated haemoglobin A1c (HbA1c)] and CVD risk factors [atherogenic index ratio, the ratio of total cholesterol (TC) / high-density lipoprotein cholesterol (HDL-C) (TC/HDL-C), TC, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), non-HDL-C, high-sensitivity C-reaction protein (hs–CRP), and blood pressure]. The trial undertook the per-protocol analysis on these clinical phenotypes for the T2DM with obesity patients who completed the 12 weeks MNT and CDT intervention.

The secondary outcome focused on the effect of genetic variants on the clinical phenotypes at the trial endpoint. The genetic predispositions of SNPs relevant to T2DM, namely, Pro12Ala SNP in *PPARG*, Leu162Val SNP in the *PPARA*, and Gly482Ser SNP in *PPARGC1A,* were analysed.

The tertiary outcome aimed to investigate the *PPARs* target genes expression associated with clinical phenotypes at the trial endpoint. The target genes were chosen from the PPARs pathway that regulates FAO and inflammation.

The quaternary outcome pursued to verify whether the DNA methylation profile in the promoter region of PPARs coactivator, *PPARGC1A,* would significantly change at the trial endpoint. The modulation of the methylation profile was further analysed for its association with the gene expressions.

The tertiary and quaternary were reversible molecular changes corresponding to the MNT and CDT intervention.

PPARs are known to be tissue-specific. Regularly, invasive biopsy procedures are involved and may not always be feasible in human subjects for ethical reasons. PBMCs are a subset of white blood cells, mainly consisting of monocytes and lymphocytes, and are known as a surrogate tissue for skeletal muscle, adipose tissue, breast, lung and liver.

In line with the primary, secondary, tertiary and quaternary outcomes, the current research had recruited three different categories of participants. The obese T2DM patients were recruited for the MNT intervention study, the lean non-T2DM participants were recruited as a control group to establish the baseline study for gene expression, and the obese bariatric patients were recruited for the validation study. PBMC will be used for intervention and baseline studies. The skeletal muscle, VF and SF tissue were obtained as by-products from the laparoscopic bariatric surgery, and the peripheral blood was withdrawn from the bariatric obese patient to validate the suitability of PBMC as a surrogate for the skeletal muscle, VF and SF tissue.

1.2 Statement of Research Problem

Despite strong advocacy for a structured lifestyle intervention such as MNT for weight loss and as the cornerstone of clinical care for the management of diabetes and CVD risk factors, adherence is often poor, as only 16.4% of T2DM Malaysians (Hussein *et al.*, 2013) and 30% globally (Martin *et al.*, 2005) found to adhere to dietary regimen; and the rising prevalence of T2DM is evident. Poor adherence to lifestyle intervention contributes significantly to T2DM and CVD events. The molecular mechanism supporting the clinical outcome from MNT is scarce and may limit the efficacy of the clinical application.

1.3 Study Significance

The incorporation of pharmacology agonists such as PPARA (fibrate) and PPARG (thiazolidinediones) have been known to induce a hypolipidemic effect, improve insulin sensitivity and reduce inflammation. However, activation of a PPAR pathway, particularly using PPARG agonist, is known to trigger numerous adverse health effects. To date, there has been no report on the association of MNT intervention with the virtue of pharmacological PPARs and *PPARGC1A* pathway, particularly from genetic to epigenetic perspective.

The assimilation of meal replacement therapy (MRT) and macronutrient adaptation as part of MNT intervention had increased adherence to over 80%, a tangible improvement from previously adherence reported. MRT integration is a practical way to enhance adherence to MNT algorithm regimes, especially in the context of a proficient translation of the MNT algorithm to Asian countries like Malaysia.

Uncover the molecular events occurring in T2DM based on the susceptibility of the genetic and the reversibility of certain inheritable traits such as epigenetic mark could facilitating a more efficient application of MNT as a first-line treatment for T2DM and a better diagnostic, treatment and eventually prevention to T2DM and obesity, both at individually and at the community level.

1.4 Conceptual Framework

The conceptual framework of molecular modulation of MNT in obese T2DM is depicted in Figure 1. In addition to genetic variation, alteration of the epigenetic mark, particularly in DNA methylation profile, are known to modulate genes expression that associate with clinical phenotype. The study has shown that obese T2DM are dysregulated in *PPARs* and *PPARGC1A* hypermethylated in the promoter region. The current study incorporated diet amendment for the MNT arm. The amendment comprised of two MRT for breakfast and lunch, a snack and a food-based meal plan to achieve a healthy energy deficit diet algorithm among obese adults with T2DM. The primary outcome following the MNT was body weight loss and its association with glycaemic control and CVD risk factors.

We hypothesised that the epigenetic change of DNA methylation on the *PPARGC1A* promoter region is significantly contributing to the favourable improvement of the primary outcomes through the gene regulation of target genes affiliate with PPARs FAO and inflammatory pathway. We anticipate to observe certain interactions with genetic predisposition associating with clinical phenotypes, especially in the CDT arm. We sought to evaluate whether genetic or epigenetic has a greater effect on the clinical phenotypes outcome from MNT intervention. We projected that PBMC could be an ideal surrogate for tissue-specific *PPARs* gene regulation and DNA methylation *PPARGC1A* in the promoter region to validate the PBMC finding of the current study.

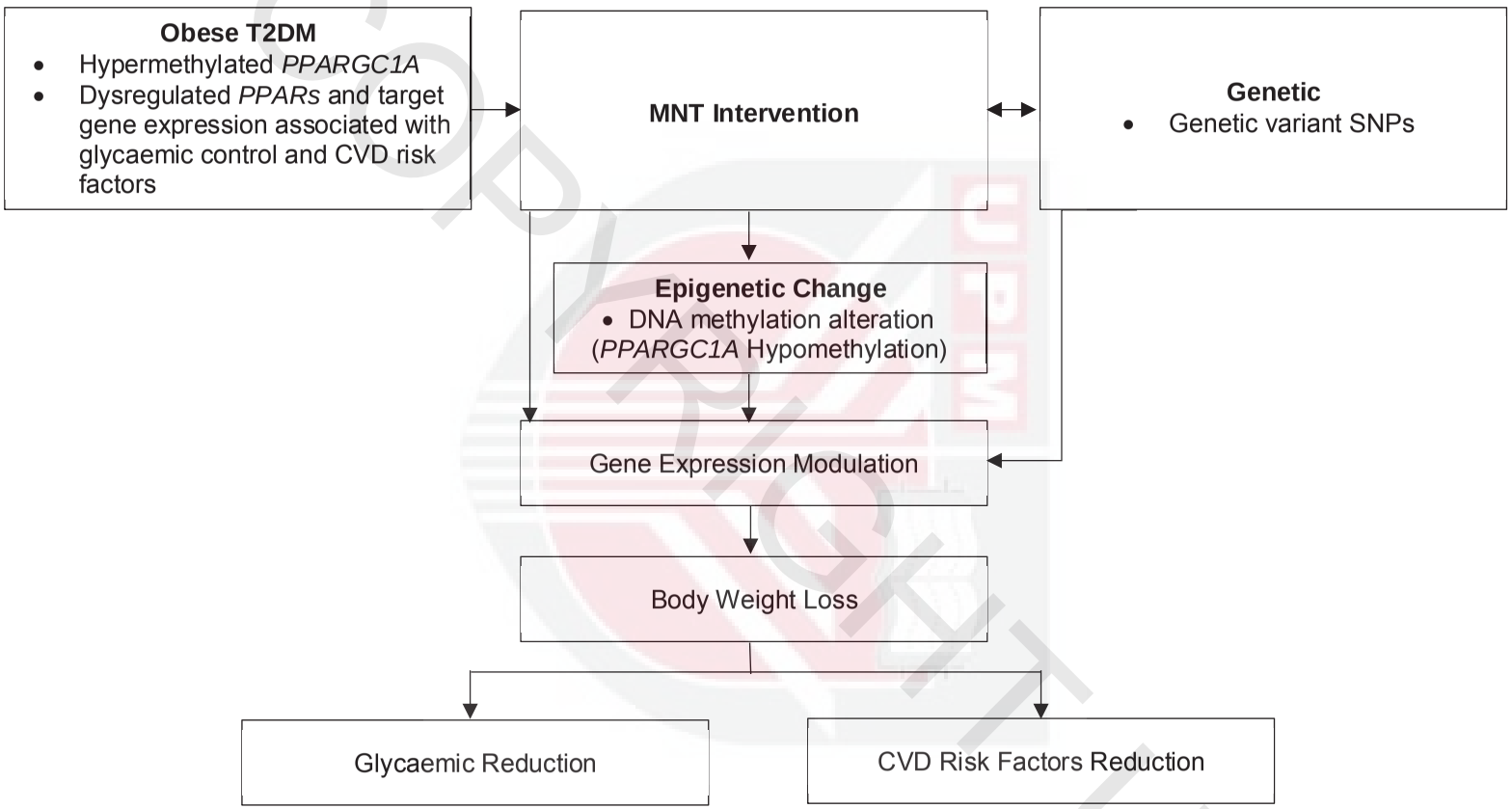

Figure 1: Conceptual Framework of molecular modulation of MNT in obese T2DM

1.5 Study Objectives

1.5.1 General Objectives

To ascertain whether genetic variant SNPs of *PPARG* Pro12Ala, *PPARA* Leu162Val and *PPARGC1A* Gly482Ser or/ and epigenetic DNA methylation changes on *PPARs* and allied transcriptional target genes network has a more predictive role on the improvement of weight loss, glycaemic index and CVD risk factors in obese patients with T2DM undertook MNT intervention. To validate the role of PBMC as a surrogate for the tissue-specific nature of PPARs.

1.5.2 Specific Objectives

1. To determine the effectiveness and association of body weight changes with the glycaemic control (HbA1c) and CVD risk factors (TC/HDL-C, TC, LDL-C, TG, non-HDL-C, hs-CRP and blood pressure) from MNT versus CDT in obese T2DM at 12-week.

2. To determine the association of SNPs *PPARG* Pro12Ala, *PPARA* Leu162Val and *PPARGC1A* Gly482Ser with the changes of body weight, glycaemic control and CVD risk factors from MNT versus CDT in obese T2DM at 12-week.

3. To determine the baseline characteristic of *PPARs* and *PPARGC1A* target genes expression involve in FAO and inflammatory pathway in obese T2DM and lean non-T2DM.

4. To determine the association of *PPARs* and *PPARGC1A* target genes expression involve in FAO and inflammatory pathway with the body weight, glycaemic control and CVD risk factors outcome changes from MNT versus CDT in obese T2DM at 12-week.

5. To determine the DNA methylation profile changes on the promoter region of *PPARGC1A* from MNT versus CDT in obese T2DM at 12-week.

6. To determine the association of DNA methylation profile on the promoter region of *PPARGC1A* with the gene expression, body weight, glycaemic control and CVD risk factors outcome changes from MNT versus CDT in obese T2DM at 12-week.

7. To elucidate whether DNA methylation profile on the promoter region of *PPARGC1A* as well as *PPARs* and *PPARGC1A* genes expression in PBMC associate with skeletal muscle, VF and SF in obese bariatric participants.

1.6 Hypothesis

1. MNT would reduce body weight, glycaemic control and CVD risk factors in obese T2DM at 12-week. The body weight changes would significantly associate with the improvement of glycaemic control and CVD risk factors in obese T2DM at 12-week.

2. MNT would induce favourable changes in body weight, glycaemic control and CVD risk factors, irrespective of its association of SNPs *PPARG* Pro12Ala, *PPARA* Leu162Val and *PPARGC1A* Gly482Ser in obese T2DM at 12-week.

3. Obese T2DM would show lower expression of *PPARs* and *PPARGC1A* target genes expression involved in FAO and inflammatory pathway compared to lean non-T2DM.

4. The *PPARs* and *PPARGC1A* target genes expression involved in FAO and inflammatory pathway would associate with the body weight, glycaemic control and CVD risk factors outcome changes from MNT in obese T2DM at 12-week.

5. The MNT would reduce the DNA methylation profile changes on the promoter region of *PPARGC1A* from MNT in obese T2DM at 12-week.

6. The DNA methylation profile on the promoter region of *PPARGC1A* would associate with the gene expression, body weight, glycaemic control and CVD risk factors outcome changes from MNT in obese T2DM at 12-week.

7. PBMC would associate with the DNA methylation profile on the promoter region of *PPARGC1A* as well as *PPARs* and *PPARGC1A* gene expression in skeletal muscle, VF and SF in obese bariatric participants.

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