UNIVERSITI PUTRA MALAYSIA

CORRELATION OF VITAMIN D AND E PLASMA LEVELS WITH THE PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS AMONG ADULTS IN SELANGOR, MALAYSIA

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FPSK(m) 2018 9

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

January 2018

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master Science

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Faculty : Medicine and Health Sciences

Poor glycemic status instigated by derangement of insulin signalling mechanism is the leading cause of Type 2 Diabetes Mellitus (T2DM) pathophysiology. Classical risk factors such as obesity, increasing age, sedentary lifestyle and metabolic syndromes have strong association with T2DM. Recent evidence indicates plasma level of vitamin D and E may alter insulin sensitivity to the cells, but its pathophysiology to diabetes remains unclear. The study was aimed to investigate the potential correlation of plasma level of vitamin D and E with glycemic status in T2DM pathophysiology. A cross-sectional study involved 50 DM and 50 non-DM respondents were recruited through convenient sampling. Socio-demographic, medical background, anthropometric measurement and lifestyle behaviours were the risk factors of diabetes and association of plasma level vitamin D and E were the new risk factors that proposed in the current study. SPSS version 22.0 was adopted for the statistical analysis and significant value was set at $P<0.05$. The outcome of study highlighted poor glycemic status in DM group (9.32±2.61%) with significant different with non-DM (6.67±2.01%) group. The association of poor glycemic status with gender, level of education, ethnicity and family history who is having diabetes were statistically significant ($P<0.05$) in DM group. Glycemic status [(haemoglobin A1c (HbA1c) and fasting blood glucose (FBG)] and lipid profiles status [high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol (TC)] were significantly different between DM and non-DM groups. Most of the respondent were deficient of plasma vitamin D with mean value 3.43±2.95 ng/mL in non-DM group and 4.44±5.86 ng/mL in DM group which accounted about 82% and 84% respondent in respective groups. Further bivariate analysis with the group of deficiency of vitamin D (<20 ng/mL) with glycemic status (<7% and >7% of HbA1c

level) revealed strong association ($P<0.05$) of deficiency of vitamin D with poor glycemic status (HbA1c and FBG) in DM groups. Lipid profile status (LDL, HDL and TC) were significantly higher ($P<0.05$) in non-DM group. The calcium level in non-DM was 8.11 mg/dL and DM group was 9.57 mg/dL. Glycemic status (HbA1c, FBG and C-Peptide) and lipid profile status (LDL and HDL) were significantly associated ($P<0.05$) with calcium plasma level. The distribution of total vitamin E (VE) in plasma was evidently higher in DM group (4.9±4.3 µg/mL) compared to non-DM group (3.97±3.33 µg/mL). Furthermore, the relationship of total VE with deficiency of vitamin D has significantly associated in poor glycemic status ($P<0.05$) in DM group. At higher level of total VE (>4.9 µg/mL), there was poor glycemic status in DM group. Concurrently, lipid profiles status suggested LDL, HDL and TC were also significantly higher ($P<0.05$) in DM group at high level of total VE (>4.9 µg/mL). In conclusion, the present study suggested that predisposing of multiple risk factors of T2DM which predominate in poor glycemic status have strong association with deficiency of vitamin D and elevated plasma vitamin E amongst diabetic respondents. Thus, the elucidation of association of vitamin D and E in current study define the involvement of vitamin D in insulin signalling and the role of vitamin E in quenching free radical which both are interplay in T2DM pathophysiology.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KORELASI PARAS PLASMA VITAMIN D DAN E TERHADAP PATOFISIOLOGI DIABETES MELITUS JENIS 2 DI KALANGAN RESPONDEN DEWASA DI SELANGOR, MALAYSIA

Oleh

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Status glisemik yang lemah disebabkan gangguan mekanisme isyarat insulin adalah faktor utama dalam patofisiologi Diabetes Mellitus Jenis 2 (DMJ2). Faktor risiko yang biasa seperti obesiti, peningkatan usia, gaya hidup sedentari dan sindrom metabolik telah dikaitkan dengan DMJ2. Bukti terkini menunjukkan tahap plasma vitamin D dan E boleh mengubah sensitiviti insulin kepada sel-sel, tetapi patofisiologinya kepada diabetes masih kurang jelas. Kajian ini dijalankan bertujuan untuk melihat potensi korelasi paras plasma vitamin D dan E dengan penilaian status glisemik dalam patofisiologi DMJ2. Kajian rentas melibatkan 50 orang DM dan 50 orang bukan DM telah direkrut menggunakan persampelan mudah. Faktor risiko seperti sosio-demografik, latar belakang perubatan, ukuran antropometri dan cara hidup adalah faktor penyumbang penyakit diabetes dan hubung-kait dengan paras vitamin D dan E dalam plasma adalah faktor terbaru dicadangkan dalam kajian ini. SPSS versi 22.0 telah digunakan untuk analisa kajian ini dan nilai signifikan ialah $P<0.05$. Hasil daripada kajian ini menunjukkan status glisemik yang lemah dalam kumpulan DM (9.32±2.61%) dan bukan DM (6.67±2.01%) dengan perbezaan yang signifikan. Paras glisemik yang lemah juga berkait rapat dengan faktor jantina, latar belakang pendidikan, bangsa dan sejarah keluarga yang mempunyai penyakit diabetes dengan signifikan ($P<0.05$) dalam kumpulan DM. Hasil kajian ini juga menunjukkan perbezaan yang signifikan terhadap paras glisemik [*haemoglobin A1c* (HbA1c) dan gula darah semasa berpuasa (FBG)] dan status profil lipid [lipoprotein berketumpatan tinggi (HDL), lipoprotein berketumpatan rendah (LDL) dan kolesterol total (TC)] di antara kumpulan DM dan bukan DM. Kebanyakan responden menunjukkan kekurangan vitamin D dengan purata 3.43±2.95 ng/mL dalam kumpulan bukan DM dan kumpulan DM ialah 4.44±5.86 ng/mL di mana keduanya-duanya menunjukkan peratusan 82% dan 84% masing-masing. Analisa bivariate di antara kumpulan yang kekurangan vitamin D (<20 ng/mL) dengan status glisemik (paras HbA1c <7% dan >7%) telah menunjukkan hubung-kait yang kuat

dalam kumpulan DM yang mempunyai paras glisemik yang rendah dan kurangnya vitamin D. Status profil lipid (LDL, HDL dan TC) menunjukkan peningkatan yang signifikan dalam kumpulan bukan DM. Paras kalsium dalam kumpulan bukan DM adalah 8.11 mg/dL dan DM adalah 9.57 mg/dL. Status glisemik (HbA1c, FBG dan C-Peptide) dan status profil lipid (LDL dan HDL) mempunyai hubung-kait yang kuat dengan paras kalsium dalam plasma. Distribusi vitamin E total (VE) dalam plasma adalah terbukti lebih tinggi dalam kumpulan DM (4.9±4.3 µg/mL) berbanding dengan kumpulan bukan DM (3.97±3.33 µg/mL). Tambahan pula, hubungan VE total dengan kekurangan vitamin D mempunyai hubung-kait yang kuat ($P<0.05$) dalam status glisemik yang lemah dalam kumpulan DM. Kumpulan DM menunjukkan status glisemik yang lemah pada paras VE total lebih tinggi daripada 4.9 µg/mL. Pada masa yang sama, status profil lipid mencadangkan LDL, HDL dan TC juga meningkat secara signfikan dalam kumpulan DM pada paras VE total lebih tinggi daripada 4.9 µg/mL. Kesimpulannya, kajian ini mencadangkan faktor yang pelbagai dalam DMJ2 mempengaruhi status glisemik yang lemah dan menyebabkan hubung-kait yang kuat dalam kekurangan vitamin D dan peningkatan vitamin E dalam plasma di antara responden pesakit diabetes. Oleh sebab itu, hubung kait dengan vitamin D dan E diterjemahkan sebagai penglibatan vitamin D dalam isyarat insulin dan peranan vitamin E untuk memerangkap radikal bebas di mana kedua-duanya saling bekerjasama dalam patofisiologi DMJ2.

ACKNOWLEDGMENTS

In the Name of Allah, the Most Gracious, the Most Merciful

Thanks to Allah, the Merciful Lord for all the countless blessings you have offered me, and thanks to my mother (Junaidah binti Kamal) and father (Md Razip bin Manan) for their love and support. I would also like to thank my brother (Md Luqman Hakim), sister (Amirah) and friends whose value to me only grows with age and owe them much time. A special thanks to all academics that supports me throughout all semesters.

My deep gratitude goes first to Allahyarham Assoc. Prof Dr Mohd Sokhini Abd Mutalib who expertly guided me through my graduate and who shared the enthusiasm of three years of discovery. His unwavering assisting for Biochemistry and Nutritional Science subject kept me constantly engaged with my research and his personal generosity helped make my time at Biochemistry and Nutrition Laboratory enjoyable. Also, I would like to express my appreciation and be thankful to Dr Huzwah Khaza'ai for her patience and knowledge in reviewing and correcting the thesis. Her supports, guidance and encouragement keep me a positive environment to do science lively. Besides, my co-supervisor, Dr Muhammad Mikhael Joseph and Assc. Prof Dr Azrina Azlan for allowing me to collect data in Serdang Hospital and advised on clinical study. Their devotion in sharing clinical knowledge is highly appreciated. Also, I would like to express my appreciation to Dr Syahida Ahmad from Faculty of Biotechnology and Biomolecular Sciences who endlessly motivate me in research field.

My appreciation also extends to my fellow friends: Nadia Ibrahim, Afifah Jalil, Aisya Chiroma, Go Huifang, Amira Zaulkeffli, Asma Zaini, Somy Hosseini, Qais Jarrar, Henna, Sarah, Rohana Ishak, and Mr Zainal for encouraging and guiding me throughout laboratory work. Thanks also Mr Hasbullah for mentoring me on laboratory teaching especially in High Performance Liquid Chromatography (HPLC) machine.

I would like to express this journey of study with Ibn al-Haytam sayings:

"*Thus the duty of the man who investigates the writings of scientists, if learning the truth is his goal, is to make himself an enemy of all that he reads, and, applying his mind to the core and margins of its content, attack it from every side.*"

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

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LIST OF ABBREVIATIONS

Al	Adequate intake
ADA	American Diabetes Association
AGEs	Advanced Glycation End products
α-TCP	Alpha-tocopherol
α-T3	Alpha-tocotrienol
β-TCP	Beta-tocopherol
β-T3	Beta-tocotrieonol
CYP24A1	24-hydroxylase
CYP2B1	Cytochrome P450 2B1
CHD	Coronary Heart Disease
□-TCP	Delta-tocopherol
δ-TCP	Delta-tocotrienol
DBP	D-binding protein
EAR	Estimated Average Requirement
FBG	Fasting blood glucose
FIVE	Familial Isolated Vitamin E
FGF-23	Fibroblast Growth Factor-23
FVO	Fructosyl valine oxidase
□-TCP	Gamma-tocopherol
γ-T3	Gamma-tocotrienol
GLUT4	Glucose Transporter 4
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
IDF	International Diabetes Federation
IRS	Insulin Receptor Substrate
IRS-1	Insulin receptor substrate-1
LDL	Low density lipoprotein
NADPH	Nicotinamide adenine dinucleotide phosphate

NHANES	National Health & Nutrition Examination Survey
NF-kB	Nuclear factor kappa beta
NDR	National Diabetes Registry
POD	Horseradish peroxidase
P13K	Phosphatidylinositol-3-Kinase
PKCC	protein kinase c gamma
RNI	Recommendation Nutrient Intake
RDA	Recommended Daily Allowance
RXR	Retinoid X Receptor
Ser	Serine
TG	Triglycerides
TC	Total cholesterol
T2DM	Type 2 Diabetes Mellitus
Tyr	Tyrosine
UVB	Ultraviolet B ray
Vitamin D3	Cholecalciferol
Vitamin D2	Ergocalciferol
VDR	vitamin D receptor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Study background

Diabetes is a non-communicable disease with devastating, yet preventable consequences. It is characterized by high blood glucose level resulting from the defects in insulin production, insulin action or both (Boden & Laakso, 2004; McArdle et al, 2013). Insulin is a polypeptide hormone that secreted by β-cells islet of Langerhans in the pancreas in response to the glucose concentration in the bloodstream (Summers, 2006). In Asian countries, the rate of Type 2 Diabetes Mellitus (T2DM) contributes more than half the percentage of the world's diabetic population as the prevalence of diabetic patients is increasing gradually over the past few decades (WHO, 2016). According to Malaysian National Health Morbidity Survey 2015 (NHMS), there is a relative increased from 2011 (15.2%) to 2015 (17.5%) patients diagnosed with diabetes mellitus. Risk factors such as family history of diabetes, overweight, physical inactivity, increasing age, ethnicity, impaired glucose tolerance (IGT), and inadequate supplement intake have been associated with T2DM. On the other hand, metabolic syndrome such as dyslipidemia, cardiovascular disease and hypertension could lead to T2DM pathogenesis (Semenkovich & Heinecke, 1997).

Diabetes Mellitus is a condition where glucose utilization by the cells are impaired due to decrease sensitivity of the cells to insulin, termed as insulin resistance (Pørksen et al., 2002). Thus, glucose is unable to use as energy in the cells and caused the increasing glucose in the bloodstream, which known as hyperglycemia. Diagnosis of glycemic status for diabetic patient which is reflecting the glucose concentration in the blood such as fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c) are the prominent clinical diagnosis test for diabetes. The hyperglycemia happens once HbA1c level is more than 7% (WHO, 2016) which refer as poor glycemic status. Accuracy of blood measurement is essential since the blood glucose concentration is affected by food intake in individual, medications and metabolic syndromes of individuals (Sacks, 2012). FBG is suitable for the pre-diagnosis of diabetes. Yet, HbA1c was the gold standard of glycaemic index and essential in blood monitoring due to the glycated red blood cells bound within 3 months which exhibited the consistency of results for clinical standard diagnosis of diabetes mellitus (Banerjee & Chakraborti, 2014; Bose et al., 2013; Iram et al., 2013).

Lipogenesis, a consequence of impaired glucose utilization followed by the influx of free fatty acids (FFA) into the bloodstream providing the alternative energy state during prolonged starvation particularly in the brain (Wilcox, 2005; Denton et al., 1981). It is a major contribution in lipid impairment. Nevertheless, insulin resistance

that occurs in the liver is different than in adipose tissue. As adipose tissue liberates FFA into the blood for energy expenditure, liver elevates FFA flux to promote synthesis of hepatic very low-density lipoprotein (VLDL) (Grundy, 2004). The mechanism of action may contribute to the elevation of triglycerides known as hypertriglyceridaemia which is a common condition in T2DM (Krauss & Siri, 2004).

Metabolic risk factor in T2DM, is associated with the high level of triglycerides (TG), low-density lipoprotein (LDL), total cholesterol (TC) and low level of high-density lipoprotein (HDL). These lipid abnormalities exhibited an atherogenic pattern risk. Atherogenic is the process of abnormal fatty lipid mass forming plaque in the arterial wall (Carmena et al., 2004). The changes of abnormalities influence the development of insulin resistance where efflux of free fatty acids from adipose tissue increased and impaired insulin-mediated skeletal muscle uptake of free fatty acids in the liver (Boden, 1997; Kelley & Simoneau, 1994). Extensive epidemiologic studies related to lipidomic abnormalities with T2DM pathogenesis has been reported (Chen & Tseng, 2013; Fisher et al., 2012; Krauss, 2004; Mazière et al., 2004; Sorrentino et al., 2010). As the higher incidence of T2DM is highly associated with plasma lipid level, these metabolic markers which are LDL, HDL, TG and TC also were measured in current study.

Recent evidence indicates that vitamin D (Afzal et al., 2013) and vitamin E study (Wright et al., 2006) may alter glucose metabolism, which suggests that it may play a role in T2DM incidence. Generally, the human body needs little amount of vitamins but sufficient for proper functioning of the whole body's system. However, the deficiency of vitamins may contribute to metabolic syndrome such as diabetes and obesity (Krauss & Siri, 2004; Meigs, 2009). Among the various complication of T2DM, vitamin deficiency and imbalance have been associated with decrease defence against oxidative stress and impaired immune system (Rains & Jain, 2011). Although observational studies support pancreatic β cell dysfunction and insulin resistance as pathways by which vitamin D and E influence to modulate glucose homeostasis, understanding of mechanism involved in systemic inflammation remains obscure.

Vitamin D deficiency may play a functional role in many of the mechanisms related to the pathophysiology of T2DM. Although these mechanisms are not well understood, it has been proclaimed these pathways by which low vitamin D may elevate risk of diabetes via impairment of pancreatic β-cell function and increased insulin resistance. Indeed, low level of serum vitamin D has been associated with high blood glucose level in T2DM (Shenoy et al., 2014). It is postulated that the presence of sufficient level of vitamin D may stimulate insulin receptor of cells as well as inhibit pancreatic beta cells from over-secreting insulin when the level of vitamin D is low (Kadowak & Norman, 1984). Furthermore, vitamin D mechanism has indirect interaction with calcium level. Optimum vitamin D plasma level may reduce insulin resistance probably through its interaction with calcium at the parathyroid gland through regulation of the insulin receptor gene (Talaei et al.,

2013). Parathyroid hormone involved in regulation of calcium homeostasis, whereby increase activated form of vitamin D in the kidney, will stimulate the calcium absorption from gastrointestinal tract and calcium bone resorption (Heaney, 2008). Undoubtedly, calcium deficiency also has an effects on the level of vitamin D, where it could interrupt the insulin secretion in pancreas and causes the decrease of the amount of glucose transported into cell by glucose transporter (Williams et al., 1990; Zemel, 1998). It has also been reported in retrospective and cohort studies, plasma calcium level is lower in diabetic patients (Isaia et al, 2001; Colditz et al., 1992; Liu et al., 2005.; Pittas et al., 2006; Dam et al., 2006).

In parallel to it, the association of vitamin E plasma level and impairment of insulin action has been reported extensively (Nobili et al., 2006; Pittas et al., 2007; Pazdro & Burgess, 2010). The antioxidant properties of vitamin E could highlight the pathophysiological effects involving oxidative stress and inflammation that contributes to T2DM (Murase et al., 1998; Tavan et al., 1997). In diabetes, various source of free radicals contribute to the pathogenesis of tissue damage that could interrupt insulin mechanism and glucose homeostasis (Oberley, 1988). In Finland, a low intake of vitamin E has been shown to be a contributing factor of T2DM involving men aged between 42 to 60 years, where after a four years follow up, 5% of the subjects was found to be diabetic (Salonen et al., 1995). Furthermore, previous study indicates the consistency of data on the α-tocopherol level in plasma which has strong association with the pathogenesis of T2DM which could be used as a metabolic indicator (Gey et al., 1991; Mangialasche et al., 2012; Pazdro & Burgess, 2010). It is an interest of the present study to determine the relationship of vitamin D and E plasma level status with the glycemic status in non-diabetic (non-DM) respondents and diabetic (DM) patients.

1.2 Problem statement

T2DM is a complex multifaceted problem that requires extensive research in *in-vivo* and *in-vitro*. Although important knowledge has been acquired on the etiology of diabetes, understandings on precise etiopathogenesis warrant further insight. Inflammatory factors, reactive oxygen species and autoimmune reactions have all strongly emerged as the major pathogenic effectors for diabetes. Poor glycemic status has been well associated with socio-demographic, medical background, anthropometric measurement and lifestyle behaviours which are the classical risk factors and associated with the other metabolic syndromes.

Despite the superficial risk that is associated with the pathogenesis of T2DM, nutrition factors emerge as the major underlying factor. Evidences from various *in-vitro* and *in-vivo* studies point to the significant important of micronutrient effects such as vitamins and mineral in comprehending the mechanism in the development of T2DM. Although recent cross-sectional studies may produce an indicative data to suggest a positive association between vitamin D and E with insulin resistance, yet they were inadequate to substantiate the cause and effect in addressed problem.

Nevertheless, emerging evidence on the involvement of vitamin D and E and T2DM development summon further insight. The present study is interested to evaluate the association of vitamin D and E plasma level with T2DM pathophysiology. On the other hand, the association of biochemical parameters such as plasma lipid profile (TG, TC, LDL and HDL) with vitamin D and E may lead to T2DM incidence. Numerous studies reporting on the lipid profile data in diabetic patients, however, the data on lipid profile with vitamin D and E related with diabetes mellitus has not yet reported in Malaysia.

This present study was conducted to investigate the relationship between insulin impairment and deficiency of plasma level of vitamin D and E as a potential risk factor of increasing predisposing T2DM pathophysiology. In addition, the socio-demographic, medical background, anthropometric measurement, lifestyle behaviors and biochemical measurement associated with vitamin D and E is believed to have a significant effect as their pivotal role in diabetes mellitus pathophysiology. The outcomes of this study may provide the baseline for a further intervention study on micronutrients vitamins especially for diabetic patients in Malaysia.

1.3 Significance of the study

Deficiency of vitamin D and E levels in plasma should be further insight among Malaysian diabetics population which may not fully supplicated with poor glycemic status. This study and its findings were conducted to bridge the understandings of T2DM pathophysiology despite adequate sun exposure in Asian region country (vitamin D supplementation) and daily palm oil intake in the diet among Malaysian (vitamin E supplementation). Thus, the present study could suggest the significant leading cause of diabetes mellitus among adult diabetic patients in Selangor which represent the prevalence of Malaysian. Furthermore, the data summoned up findings for future intervention study among diabetic patients and references for physician, nutritionist and health care professionals in providing the appropriate guidelines for patients.

1.4 Objectives

1.4.1 General objective

This study aims to determine and compare the factors associated with plasma vitamin D and E levels in pathophysiology of Type 2 Diabetes Mellitus (T2DM) among respondents in Selangor.

1.4.2 Specific objectives

1. To assess and compare the socio-demographic characteristics (age, gender, medical characteristics, medical backgrounds, anthropometric measurement, lifestyle behaviours and biochemical measurements (lipid profile and glucose profile) in non-DM and DM groups.
2. To determine and compare the following relationship biochemical parameters in:
   a. Groups (non-DM and DM).
   b. Socio-demographic (age, gender and race) factors.
   c. Anthropometric measurement factors.
3. To determine the association of plasma vitamin D and calcium levels in non-DM and DM groups.
4. To determine the association of total vitamin E in non-DM and DM groups.
5. To determine the contribution of socio-demographic, medical background, anthropometric measurement and biochemical parameters towards the plasma vitamin D and E levels in non-DM and DM groups with T2DM pathophysiology.

1.5 Hypotheses

1. Low vitamin D and calcium in plasma levels have association with the level of glycemic status (HbA1c).
2. Low total vitamin E in plasma level has association with the level of glycemic status (HbA1c).

1.6 Conceptual Framework:

Figure 1.1 adopted the conceptual framework of the present study. The independent variables are socio-demographic characteristic (age, gender and ethnicity), medical background, anthropometry measurement, lifestyle behaviors and biochemical parameters were influenced by the glycemic status among diabetic people. The dependent variables are plasma vitamin D and calcium as well as plasma vitamin E. The purpose of the present study is to determine the association between the independent and dependent variables among respondents in non-DM and DM groups with T2DM in public hospital and university in Serdang, Selangor. Besides, all the variables are assessed based on HbA1c level.

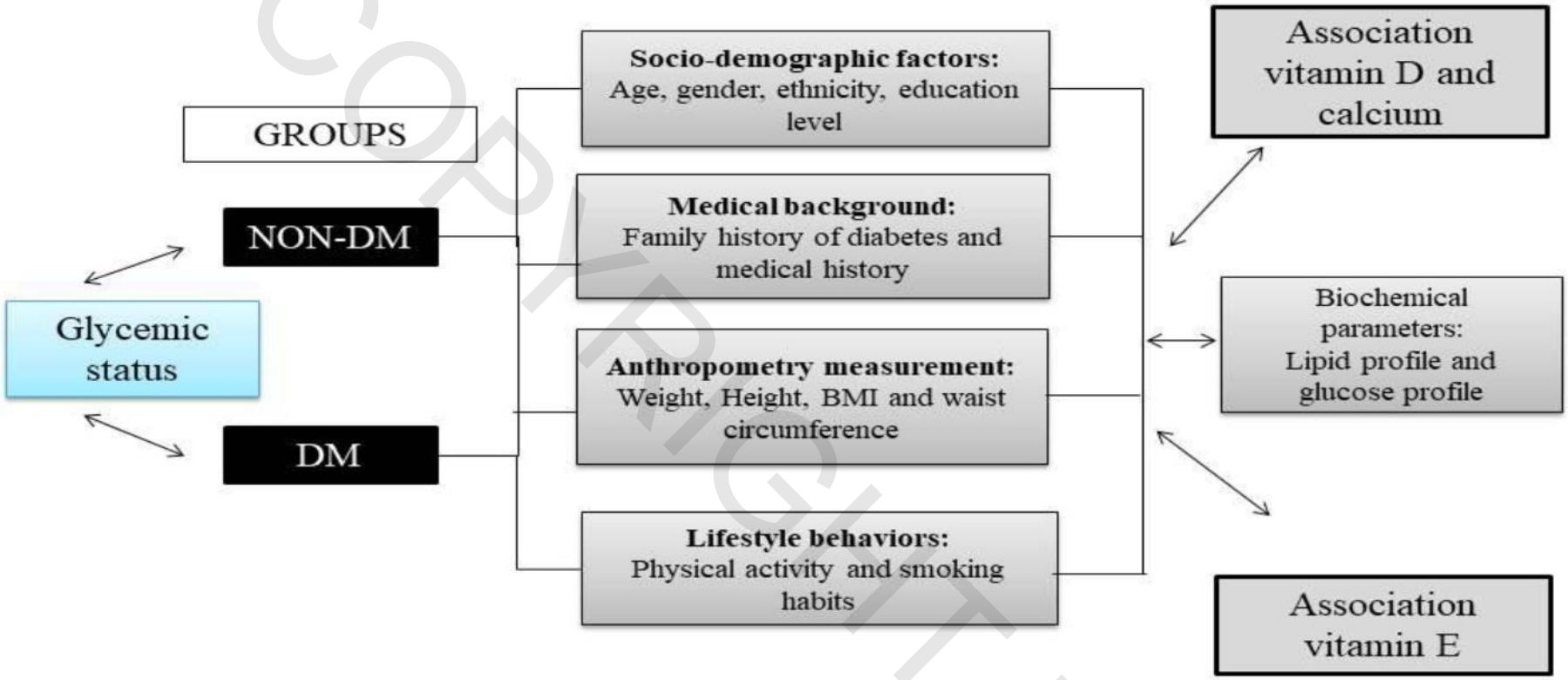

Figure 1.1 : Conceptual framework of factors associated with vitamin D and E
Socio-demographic, medical background, anthropometric measurement and lifestyle behaviors are the multiple risk factors were influenced by the glycemic status that lead to the association of deficiency vitamin D and E level in plasma with the biochemical parameters measured

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