UNIVERSITI PUTRA MALAYSIA

METABOLIC SIGNATURE OF PROTEIN ENERGY WASTING AMONG MALAYSIAN HEMODIALYSIS PATIENTS

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By

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Faculty : Medicine and Health Sciences

End-stage renal disease (ESRD) patients undergoing maintenance hemodialysis (HD) often experience a state of metabolic and nutritional derangements that is highly associated with morbidity and mortality due to the protein energy wasting (PEW) disorder. Identification of PEW was recommended by International Society of Renal Nutrition and Metabolism (ISRNM) with a reported prevalence of 18-75%. However, direct quantification of muscle wasting remains unsolved for this population besides there are no consistent guidelines and standardized scoring tools in a diverse patient-wide population that making it difficult to diagnose PEW. Thus, it is prudent to identify biomarkers signature of PEW using proton nuclear magnetic resonance (^{1}H-NMR) based metabolomics approach which will assist in diagnosis of PEW. In this cross-sectional study, a total of 106 subjects of ESRD patients undergoing chronic HD were stratified into PEW (n=53) and Non-PEW (NPEW) (n=53) based on the established ISRNM criteria. Fasting predialysis plasma samples with filtration were analyzed by ^{1}H-NMR and the data acquired through by the combination of presaturation (PRESAT) and the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence were further processed using Chenomx. Multivariate data analysis and the statistical analysis were performed using SIMCA-P and the SPSS softwares to discriminate the metabolomics profiles between the two groups.

Orthogonal partial least square discriminant analysis (OPLS-DA) demonstrated the difference in metabolomics profiles between PEW and NPEW patients by the principal component 1 and indicates that PEW syndrome induced specific metabolic pattern alteration. Combination of loading plots and variable importance in projection (VIP) plots of OPLS-DA model provides the important variable that contributed to the group separation. A total of 32 metabolites were identified and quantified using Chenomx, with 18 metabolites belong to PEW

groups and 14 metabolites represented NPEW groups. Among all the metabolites analyzed using Mann-Whitney U Test, 3-hydroxybutyrate ($p<0.001$), acetate ($p=0.027$), arabinose ($p=0.029$), maltose ($p=0.021$), ribose ($p=0.041$), sucrose ($p=0.008$), and tartrate ($p=0.018$) were significantly increased ($p<0.05$) in PEW subjects whilst creatinine ($p<0.001$) was significantly decreased.

However, analysis of covariance (ANCOVA) revealed that the contribution of arabinose, maltose, ribose, sucrose and tartrate on the group discrimination might be affected by age and dialysis vintage. Besides, creatinine was also showed to be significantly correlated ($p<0.01$) with the anthropometric mid-arm muscle area (MAMA) (r_S =0.426), lean tissue mass (LTM) (r_S=0.362) and albumin (r_S=-0.315). Our results signified that patients who experienced PEW had different metabolic profiles as opposed to NPEW patients. Pathway analysis indicated that PEW-related metabolites triggered perturbation in fatty acid mechanism and induced gluconeogenesis as well as glyoxylate and dicarboxylate metabolism. These results provide primary data in understanding metabolic perturbation of PEW and corresponding abnormal metabolites that potentially serve as biomarker of PEW.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
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METABOLIK KHUSUS BAGI PENYUSUTAN PROTIN DAN TENAGA DALAM KALANGAN PESAKIT HEMODIALISIS DI MALAYSIA

Oleh

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Pesakit kegagalan ginjal peringkat akhir (ESRD) yang menjalani rawatan hemodialisis (HD) sering mengalami satu keadaan di mana berlaku gangguan metabolik dan nutrisi yang berkait dengan morbiditi dan mortaliti yang disebabkan oleh sindrom penyusutan protin dan tenaga (PEW). Identifikasi PEW telah dicadangkan oleh Persatuan Nutrisi dan Metabolisme Renal Antarabangsa (ISRNM) dengan prevalens yang dilaporkan sebanyak 18-75%. Walau bagaimanapun, kuantifikasi secara langsung bagi penyusutan otot masih tidak dapat diatasi bagi populasi ini selain ketiadaan garis panduan yang konsisten dan alat penskoran yang seragam bagi populasi pesakit yang berbeza-beza yang mengakibatkan kesukaran untuk mendiagnosis PEW. Oleh itu, adalah bernas untuk mengenalpasti biomarker khusus bagi PEW dengan menggunakan pendekatan metabolomik berasaskan proton resonans magnet nukleus (^{1}H-NMR) yang akan membantu dalam diagnosis PEW. Di dalam kajian keratan-rentas ini, seramai 106 subjek pesakit ESRD yang menjalani HD kronik dibahagikan kepada PEW (n=53) dan bukan PEW (NPEW) (n=53) berdasarkan kriteria ISRNM yang telah ditetapkan. Sampel plasma pradialisis dari pesakit yang berpuasa yang telah ditapis, dianalisis menggunakan ^{1}H-NMR dan data yang diperolehi melalui kombinasi presertasi (PRESAT) dan *Carr-Purcell-Meiboom-Gill* (CPMG) rangkaian pulsa seterusnya diproses menggunakan Chenomx. Analisis data multivariat dan analisis statistik melalui perisian SIMCA-P dan SPSS digunakan untuk mendiskriminasi profil metabolomik di antara dua kumpulan.

Analisis *orthogonal partial least square discriminant* (OPLS-DA) menunjukkan perbezaan pada profil metabolomik di antara pesakit PEW dan NPEW pada prinsipal komponen 1 dan menunjukkan bahawa sindrom PEW menyebabkan perubahan khusus pada pola metabolit. Gabungan plot pemuatan dan plot *variable importance in projection* (VIP) bagi OPLS-DA menunjukkan variabel

penting yang menyumbang kepada pemisahan kumpulan. Sebanyak 32 metabolit dikenalpasti dan dikira kuantiti menggunakan Chenomx, di mana 18 metabolit dimiliki oleh kumpulan PEW dan 14 metabolit mewakili kumpulan NPEW. Di antara kesemua metabolit yang dianalisis menggunakan *Mann-Whitney U Test*, *3-* hidroksibutirat ($p<0.001$), asetat ($p=0.027$), arabinosa ($p=0.029$), maltosa ($p=0.021$), ribosa ($p=0.041$), sukrosa ($p=0.008$), dan tartrat ($p=0.018$) menunjukkan peningkatan signifikan ($p<0.05$) pada subjek PEW manakala kreatinin ($p=0.000$) menunjukkan pengurangan signifikan.

Walaubagaimanapun, analisis kovarians (ANCOVA) menunjukkan bahawa pengaruh arabinosa, maltosa, ribosa, sukrosa dan tartrat pada pemisahan kumpulan mungkin dipengaruhi oleh umur and panjang masa dialisis. Selain itu, kreatinin juga menunjukkan signifikan korelasi ($p<0.01$) dengan kawasan otot pertengahan lengan antropometrik (MAMA) ($rs = 0.426$), jisim tisu tanpa lemak (LTM) ($rs = 0.362$) dan albumin ($rs = -0.315$). Hasil kajian ini menandakan bahawa pesakit yang mengalami PEW mempunyai perubahan metabolik yang berbeza berbanding pesakit NPEW. Analisis laluan menunjukkan bahawa metabolit yang berhubung kait dengan PEW mencetuskan perturbasi dalam mekanisme asid lemak serta mendorong glukoneogenesis dan metabolisme glioksilat dan dikarboksilat. Dapatan ini menyediakan data primer dalam memahami perubahan metabolik PEW dan metabolit abnormal sepadan yang mempunyai potensi unuk berfungsi sebagai biopenanda PEW.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

^{1}H-NMR	Proton Nuclear Magnetic Resonance Spectroscopy
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BMI	Body mass index
B/P	Blood pressure
CKD	Chronic Kidney Disease
CPMG	Carr-Purcell-Meiboom-Gill
CVD	Cardiovascular disease
DEI	Dietary energy intake
DPI	Dietary protein intake
ESRD	End Stage Renal Disease
FTM	Fat tissue mass
GC-MS	Gas Chromatography-Mass Spectrometry
GNRI	Geriatric Nutritional Risk Index
HD	Haemodialysis
HDLC	High density lipoprotein cholesterol
HGS	Handgrip strength
Hgb	Hemoglobin
hsCRP	high-sensitivity C-reactive protein
Hz	Hertz
ISRNM	International Society of Renal Nutrition and Metabolism
KDIGO	Kidney Disease: Improving Global Outcomes
Kt/V	Index of dialysis adequacy
LC-MS	Liquid Chromatography-Mass Spectrometry
LDLC	Low density lipoprotein cholesterol
LTM	Lean tissue mass
MAMA	Mid-arm muscle area
MAMC	Mid-arm muscle circumference
MHz	Megahertz
MIS	Malnutrition Inflammation Score
MVDA	Multivariate data analysis
NKF	National Kidney Foundation
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
OPLS-DA	Orthogonal Partial Least Squares-Discriminant Analysis
PATCH	Palm Tocotrienols in Chronic Hemodialysis Patients
PCA	Partial Component Analysis
PEW	Protein Energy Wasting
PLS	Partial Least Square
PLS-DA	Partial Least Square-Discriminant Analysis
ppm	parts per million
QOL	Quality of Life
SD	Standard deviation
SE	Standard error
SGA	Subjective Global Assessment
SIMCA	Soft Independent Modelling of Class Analogy
SPSS	Statistical Package for the Social Sciences

TAG	Triacylglyceride
TC	Total cholesterol
TSF	Triceps skinfold
TSP	Trimethylsilylpropanoic acid
WC	Waist circumferences
δ	Chemical shift in ppm

CHAPTER 1

INTRODUCTION

1.1 Research background

End-stage renal disease (ESRD) is an advanced stage of chronic kidney disease (CKD) that has been acknowledged as a public health problem worldwide (Yokote & Yokoo, 2017). Malaysia is reported as one of the country with ESRD prevalence per million populations that has steadily increased by 163.7% within 14 years (US Renal Data System, 2018). Hemodialysis (HD) continues to be the most common mode of therapy worldwide including Malaysia (Wong & Goh, 2018). While the dialysis therapy can assist in improving serum creatinine, albumin and prealbumin, normalises the protein catabolic rate (nPCR) as well as increases the dietary intake of patients (Mehrotra et al., 2002; Pupim et al., 2002), it is also highly associated with malnutrition and lower the quality of life (QOL) of the patients (Liu et al., 2006; Rutledge & McMahon, 2000). In fact, high incidence of malnutrition is a major contributor to morbidity and mortality in advanced CKD patients undergoing HD.

The Malaysian Dialysis and Transplant Registry rely on two nutrition-related parameters, namely BMI and serum albumin to screen HD patients for malnutrition. However, these nutritional parameters are inadequate to identify an alternate view of malnutrition known as protein energy malnutrition, or recently known as protein energy wasting (PEW) syndrome. PEW has a wide prevalent in dialysis population with 18-75% of CKD patients undergoing maintenance dialysis therapy exhibit wasting according to International Society of Renal Nutrition and Metabolism (ISRNM) proposed criteria and this has been associated with increased risk of mortality and adverse clinical outcomes in this population (Leinig et al., 2011; Kalantar-Zadeh, Ikizler, Block, Avram, & Kopple, 2003; Mehrotra & Kopple, 2001; Kopple, 1997). PEW is referred as multiple nutrition and catabolic alterations that caused a chronic decreased of protein stores and energy fuels in the body, exhibited by low body protein and fat masses (Carrero et al., 2013). Causes of PEW in HD patients are multifactorial including abnormalities in energy and protein metabolism due to uremic toxicity, metabolic acidosis, chronic inflammation, co-morbid illnesses, multiple endocrine disorder, dialysis related hypermetabolism as well as nutrient losses into dialysate that eventually leads to excess catabolism of muscle and fat (Carrero et al., 2013; Fouque et al., 2008; Gracia-Iguacel et al., 2014; Ikizler et al., 1994). Besides, ageing, poor physical activity, frailty, gender differences and patients' socioeconomic status can also contributed to the presence of PEW in dialysis patients (Carrero et al., 2013; Ikizler et al., 2013). Consequently, PEW patients usually experienced nutritional and metabolic derangement that include persistent inflammation, metabolic acidosis, gradual

weight loss and a state of hypercatabolic leading to break down of muscle and fat tissues as well as reduction of serum proteins (Carrero et al., 2013; Avesani et al., 2006). According to Carrero et al., (2013) even though dialysis reverses uremia, residual metabolic derangements, inflammation, comorbid conditions and the dialysis procedure itself may allow PEW to develop or worsen.

PEW is common in patients with CKD and is associated with adverse clinical outcomes, particularly in individuals with CKD stage G3b, G4 and G5 (eGFR<45 ml/min/1.73 m^2 of the body surface area) (Obi, Qader, Kovesdy, & Kalantar-Zadeh, 2015). This syndrome amongst HD and peritoneal dialysis (PD) patients has been a worldwide incidence since the 1990s (Kopple, 1997; Cianciaruso et al., 1995) and is correlated with the increment of mortality and morbidity cases (Sung Hee Chung, Lindholm, & Lee, 2003; Marcen, Teruel, De La Cal, & Gamez, 1997). Therefore, in 2008, the diagnosis criteria of PEW were presented by the ISRNM. According to ISRNM, PEW is diagnosed if three out of four characteristics are present; (i) low levels of body serum (albumin, transthyretin, or cholesterol); (ii) reduced body mass (low or reduced body or fat mass); (iii) reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference) and (iv) unintentional low energy and protein intake (Fouque et al., 2008). However, emerging studies are challenging the application of these parameters (Gracia-Iguacel et al., 2014; Drechsler et al., 2011; Leinig et al., 2011; Vegine, Fernandes, Torres, Silva, & Avesani, 2011) as this diagnostic criteria lacks biological validation and more intensive research to identify reliable PEW biomarkers are required.

Although no study on identifying PEW using the metabolomics approach has been carried out to date, current literature across multiple metabolomics studies have been able to identify several potential biomarkers linked to progression of CKD (Jia et al., 2008; Mutsaers et al., 2013; Qi et al., 2012; Rhee et al., 2010; Schefold et al., 2009) enabling CKD detection and prediction at much earlier stage than conventional test. This method offers the potential for a holistic approach to clinical medicine, as well as improvements in disease diagnoses and the understanding of pathological mechanisms. Therefore, we propose to use the cutting edge proton nuclear magnetic resonance (^{1}H-NMR)-based metabolomics approach to facilitate identification of plasma metabolites associated with the catabolism of muscle and fat tissues related to the facets of PEW development in Malaysian HD patients. The principal of the metabolomics techniques is to identify global small-molecule metabolite profiles from complex samples like biofluids and tissue using a non-targeted and unbiased approach (Zhao, 2013). Metabolomics measures metabolites within a biological system at a given time, and profiling of these metabolites can provide detailed information on how the disease affects the metabolites physiologically or pathologically and represents a useful tool for biomarker detection (Friedrich, 2012; Zhang et al., 2014). In view of this, metabolomics approach will serve as the primary data for a more in depth knowledge on PEW specifically related to its mechanistic explanation.

1.2 Problem statement

Traditional nutritional status measurements indicate that prevalence of PEW can be as high as 75% in dialysis population (Leinig et al., 2011). In fact, prevalence of PEW has been reported to occur in 59% of HD population in two major hospitals in Malaysia (Harvinder et al., 2016). PEW is not only interrelated with infection, CVD, frailty, and depression, but these complications may also increase the extent of PEW itself in a vicious cycle. Even worse, this syndrome of detrimental changes in nutrition and body composition lead to heightened morbidity and mortality particularly in dialysis population (Carrero et al., 2013). Due to the fact that PEW is caused by multifactorial conditions, this signify the need for a global diagnostic approach that consider a panel of biomarkers as opposed to a single biomarker in a traditional system.

The ISRNM provided guidelines in identifying PEW. However, a few studies reported that they identified less malnourished patients using diagnostic criteria proposed by ISRNM compared to the other tools (Gracia-Iguacel et al., 2014; Drechsler et al., 2011; Leinig et al., 2011; Vegine et al., 2011). According to Obi et al. (2015), studies that applied serial assessment of nutritional status using scoring tools to identified PEW patients, including the subjective global assessment (SGA), the malnutrition inflammation score (MIS) and geriatric nutritional risk index (GNRI) might have better association with hospitalization and mortality as well as nutritional and inflammatory parameters in the final stage CKD patients. These emerging studies are challenging the application of the ISRNM diagnostic criteria which have not been validated against biomarkers of metabolic changes that are underlying the catabolism of muscle and fat tissue associated with PEW. In fact, extrapolation of ISRNM diagnostic criteria to different HD population has also been questioned (Gracia-Iguacel et al., 2014).

On that account, the use of ^{1}H-NMR based metabolomics approach is postulated to facilitate identification of plasma metabolites changes associated with PEW and explain the PEW mechanism in HD population. Because metabolomics in renal practice is relatively new, literature linking metabolic parameters assessed through metabolomics platform is scarce. To the best of our knowledge, no study on identifying PEW using the metabolomics approach has been carried out to date. Therefore, it is of interest to find out the prevalence of PEW in Malaysian HD patients using the diagnostic criteria proposed by the ISRNM that works simultaneously with the metabolomics techniques. This research is also attempts to investigate the relationships of the plasma metabolic profile with conventional parameters with regards on identification of PEW.

1.3 Significance of the study

As there is no study has reported on metabolomics approach to identify PEW in HD patients, this finding will serve as the pilot and primary data for a more in depth knowledge on PEW specifically related to its mechanistic explanation and the differences in plasma metabolites between PEW and Non-PEW HD patients. The baselines data of plasma metabolic profiles of PEW patients can be established together with a discovery of new biomarkers that eventually could be used for the identification of therapeutic targets and selection of the most suitable treatment that are critical to the health status of HD patients. Likewise, new PEW metabolic diagnostic criteria will provide the basis for future work to increase awareness, identify research needs, and screen for malnutrition in patients with CKD. This is in line with Ministry of Health's National Strategic Plan for Non-Communicable Disease that emphasized on prevention, early detection and diagnosis as a cost-effective approach. This innovation will impact the society, economy and nation in the positive perspectives. It is important to search actively for diagnostic and therapeutic approach of PEW since early diagnosis and treatment can improve the prognosis for CKD patients and reduce the monetary costs connected with treatment.

1.4 Objectives

1.4.1 General objective

To identify biomarkers signature of hemodialysis patients experiencing protein energy wasting using the ^{1}H-NMR based metabolomics approach.

1.4.2 Specific objective

1. To determine demographic, anthropometric, biochemical, clinical and nutritional profiles of PEW and Non-PEW (NPEW) patients.
2. To characterize and discriminate metabolic profiles of PEW and NPEW HD patients using non-targeted metabolomics approach.
3. To identify potential biomarker of PEW and its association with ISRNM diagnostic criteria.

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