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Dietary fatty acid intake in hemodialysis patients and associations with circulating fatty acid profiles: A cross-sectional study

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ABSTRACT

Objectives: The aims of this study were threefold:
first, to assess the dietary fatty acid (FA) intake and blood FA status in Malaysian patients on hemodialysis (HD); second, to examine the association between dietary FA intakes and blood FA profiles in patients on HD; and third, to determine whether blood FAs could serve as a biomarker of dietary fat intake quality in these patients.
Methods: Using 3 d of dietary records, FA intakes of 333 recruited patients were calculated using a food database built from laboratory analyses of commonly consumed Malaysian foods. Plasma triacylglycerol (TG) and erythrocyte FAs were determined by gas chromatography.
Results: High dietary saturated fatty acid (SFA) and monounsaturated fatty acid (MUFA) consumption trends were observed. Patients on HD also reported low dietary ω-3 and ω-6 polyunsaturated fatty acid (PUFA) consumptions and low levels of TG and erythrocyte FAs. TG and dietary FAs were significantly associated respective to total PUFA, total ω-6 PUFA, 18:2 ω-6, total ω-3 PUFA, 18:3 ω-3, 22:6 ω-3, and trans 18:2 isomers ($P < 0.05$). Contrarily, only dietary total ω-3 PUFA and 22:6 ω-3 were significantly associated with erythrocyte FAs ($P < 0.01$). The highest tertile of fish and shellfish consumption reflected a significantly higher proportion of TG 22:6 ω-3. Dietary SFAs were directly associated with TG and erythrocyte MUFA, whereas dietary PUFAs were not.
Conclusion: TG and erythrocyte FAs serve as biomarkers of dietary PUFA intake in patients on HD. Elevation of circulating MUFA may be attributed to inadequate intake of PUFAs.

This work was supported by the Malaysian Government through the Malaysian Palm Oil Board. KBH and TK conceptualized the study design and wrote the manuscript. KBH, SS, AS, and MS performed the data collection. KBH and SSN performed laboratory work. KS, KBH, and TK interpreted the gas chromatograms. KC performed statistical analysis and data interpretation. KS, PK, ZAMD, GBL, AHAG, GAK, and ZM provided intellectual input and critically revised the manuscript. All authors read and approved the final manuscript. Members of PaTCH Investigators (alphabetical order) are Dr. Bee Boon Cheak (Hospital Selayang, Malaysia), Dr. Lim Soo Kun (Universiti Malaya, Malaysia), Dr. Ravindran Visvanathan (Hospital Kuala Lumpur, Malaysia), Dr. Rosnawati Yahya (Hospital Kuala Lumpur, Malaysia), and Dr. Sunita Bavanandan (Hospital Kuala Lumpur, Malaysia).
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Introduction

Patients undergoing hemodialysis (HD) treatment experience a higher risk for cardiovascular disease (CVD), which is the leading cause of death in this population [1]. This is also evident with the Malaysian maintenance HD population with proportional CVD mortality ranging between 32% and 37% reported over the past 10 y [2]. The high incidence of CVD mortality in patients on HD cannot be fully explained by traditional CVD risk factors alone [3]. Accumulating evidence reveals that biomarkers of non-traditional risk factors such as oxidative stress, inflammation, bone and mineral disorders, vascular stiffness, and protein-energy wasting are closely associated with CVD and all-cause mortality in these patients [3]. The triad of oxidative stress, inflammation, and dyslipidemia resulting from this uremic milieu is causally interconnected and plays a pivotal role in the pathogenesis of premature atherosclerosis events [4]. Recent evidence also suggests that the circulating fatty acid (FA) profile is an independent risk factor of CVD event and mortality in patients on HD [5–7].

The FA composition (FAC) of blood reflects both dietary intake and metabolism of endogenously produced FA. Abnormalities in blood FA profiles are noted in patients on HD compared with their healthy counterparts, primarily characterized by elevation of monounsaturated fatty acid (MUFA) concentrations concomitant with reduced levels of polyunsaturated fatty acid (PUFA) [8]. It is hypothesized that this altered FA profile is attributed to uremic milieu and suboptimal intake of essential FAs [8]. In this context, knowledge gaps exist on the effect of dietary exposures leading to the endogenous incorporation of FAs into blood and tissue FAC in patients on HD independent of the presence of a chronic disease state. Filling in these knowledge gaps is important to probing the mechanistic pathways of FAs metabolism influenced by the uremic state and dietary availability. On the other hand, blood FAC is also used to assess the quality of habitual dietary fat intake in observational studies and to monitor compliance in interventional studies [9]. The blood FAC overcomes the limitations of conventional dietary assessment methods such as subject underreporting, interviewer bias, incorrect portion size estimation, and availability of a food composition database with values for individual FA [10]. However, the utility of blood FAC as a biomarker of dietary FA intake under the pathologic condition in patients on HD requires further research.

We recently summarized the blood FA status of HD populations from different countries [8]. However, only a few studies had large sample sizes, and these studies originated from the United States, countries on the Sea of Japan, and Scandinavia [8]. More studies with bigger sample sizes from other regions are warranted. We also observed that geographic disparities in reported circulating FA profiles of patients on HD were likely due to the variations in dietary habits in tandem with ethnic-cultural practices [8]. Nevertheless, information on dietary FA intake was lacking in these studies, which did not allow critical cross-country comparisons. Dietary FAs do not only supply energy but are also essential for various biological functions in human health. In particular for patients on HD, specific dietary FAs, such as ω-3 PUFAs, have been reported to moderate CVD and clinical outcomes by mediating anti-inflammatory effects [11], muscle preservation [12], and secondary prevention of CVD events [13].

Clearly there is a priority to assess both the quality of dietary FA intakes and circulating FA profiles specific to the HD population at the same time. Of note, an additional feature of the present study is that this target population majorly consumes palm oil, a vegetable oil commodity produced in Malaysia. Therefore, data on the blood FA profiles assessed in this HD population will be invaluable to forming a reference data set for future comparisons to other studies of populations from different countries consuming different types of dietary fats. In line with these research needs, the present study had the following objectives:

1. Assess the dietary FA intake and blood FA status in Malaysian patients on HD.
2. Examine the association between dietary FA intakes and blood FA profiles in patients on HD.
3. Determine the ability of blood FA as a biomarker of quality of dietary fat intake in patients on HD.

Plasma triacylglycerol (TG) FA reflects dietary intake from the preceding days [10]. Therefore, we investigated the association between this biomarker and FA dietary records, which were collected within 1 wk of blood sampling. On the other hand, several studies have reported the relationship between erythrocyte FA and clinical outcomes in patients on dialysis [8]. However, the associations between dietary FA intakes and erythrocyte FA remain to be fully elucidated.

Materials and methods

Study population

The study population comprised patients initially screened for the PaTCH (Palm Tocotrienols in Chronic Hemodialysis) study, conducted from October 2015 to October 2016. Participant recruitment was from multiple dialysis centers within the urban area of the Klang Valley, Malaysia. Inclusion criteria for recruitment into this study were individuals undergoing HD, age >18 y, dialyzing for ≥3 mo, and willingness to provide fasting blood samples and dietary information. Exclusion criteria included poor adherence to HD regime, cognitive impairment, or terminal illnesses such as human immunodeficiency virus or acquired immune deficiency syndrome or malignancy. All eligible individuals signed written informed consent for this study, which received approval from the Research Ethics Committee of the National University of Malaysia and the Medical Research Ethics Committee of the Ministry of Health, Malaysia.

Dietary intake assessment

Because most dialysis centers in Malaysia do not employ dietitians [14], our research dietitians conducted face-to-face interviews with enrolled participants. Three days of dietary records (3-DDR), inclusive of a dialysis day, a non-dialysis day and one optional weekend day, were used to collect dietary information [15]. To minimize variation in data collection, all dietitians underwent training to standardize approaches for conducting interviews, using standard household measurement utensils for portion-size estimation, and patient follow-up for missing information. Because underreporting of food intake assessed using 3-DDR is common in the dialysis population and potentially affects the accuracy of dietary data obtained [16], we used the Goldberg index to identify 3-DDRs of acceptable reporters to optimize the quality of the dietary data [17]. Patients' basal metabolic rate (BMR) was estimated using the Harris–Benedict equation. Based on reported energy intake (EI), patients scoring EI-to-BMR ratios of <1.2, 1.2–2.4, and >2.4 indicated under-, acceptable-, and over-reporting of EI, respectively.

Dietary data processing

Food recalls recorded in household units in the 3-DDRs were converted to absolute weight in grams before analysis for nutrient composition using the Nutritionist Pro software (First DataBank Inc., USA). This software carries food composition databases from Malaysia and Singapore [18,19]. However, these databases lacked individual FA information. Therefore, an additional FA database of analyzed foods developed in our laboratory for a different study was referred [20]. Briefly, food samples were obtained from three different locations for each food item. Total fat extraction was carried out using Soxhlet method (Method 991.36 in AOAC 1995). Fat extracted from foods was subjected to methylation and gas chromatography as described in the next section. Based on the FA database, we determined the dietary intake of lauric acid (12:0), myristic acid (14:0), palmitic acid (PA; 16:0), palmitoleic acid (16:1 ω-7), trans-9–hexadecenoic acid (*t*–16:1 ω-7), stearic acid (SA; 18:0), trans-18:1 isomers, oleic acid (OA; 18:1 ω-9), trans-18:2 isomers, linoleic acid (LA;18:2 ω-6), α-linolenic acid (ALA; 18:3 *n*3), arachidonic acid (AA; 20:4 ω-6), eicosapentaenoic acid (EPA,; 20:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3), as well as total saturated fatty acid (SFA), total MUFA, total PUFA, total ω-3 PUFA, total ω-6 PUFA, and total trans fatty acid (TFA) in terms of both

absolute weight and percentage of total dietary fat intakes. In addition, data on serving sizes of daily fish and shellfish consumption was derived from the 3-DDRs.

FAC analyses of plasma TG and erythrocytes

Within 1 wk of obtaining participants' 3-DDRs, ~10 mL fasting blood was collected into EDTA tubes (Becton Dickinson Vacutainer, Franklin Lakes, NJ, USA) in a midweek predialysis session. Blood samples were immediately centrifuged at 3000*g* for 10 min for separation into plasma and erythrocytes. Erythrocytes were washed with normal saline and hemolyzed using distilled water, yielding erythrocyte membrane sediment [21]. Plasma and erythrocyte membrane samples were snap frozen in liquid nitrogen and stored at −80°C in a freezer until subsequent analyses within 1 y.

The FAC was determined using gas chromatography, as described elsewhere [22]. Briefly, lipids from plasma and erythrocytes were extracted using a chloroform–methanol mixture (2:1). Plasma lipids were then separated into lipid components using thin-layer chromatography with a mixed solvent phase of hexane, diethyl ether, and acetic acid (80:20:2). The TG band isolated from the thin-layer chromatography plates (Silica gel 60, Merck, Darmstadt, Germany) and lipid from erythrocytes were converted into FA methyl esters and reconstituted with hexane before injection into the gas chromatographer (Shimadzu GC-2010, Shimadzu Corporation, Japan) installed with a 100 m capillary column (SP-2560, Supelco, Bellefonte, PA, USA). Individual FAs were identified by comparing their peak retention times with known standards, and concentrations were expressed as a percentage of total peak area.

Statistical analysis

Continuous variables were presented as mean ± SD or median (interquartile range [IQR]), whereas categorical variables were presented as frequency (percentages). Dietary FA intakes were expressed as a percentage of total fat intakes for comparison against the respective individual blood FA biomarkers. Correlations between dietary FA intakes and plasma TG and erythrocytes FAC were assessed using Spearman's correlation coefficients. Partial correlations were used to assess the associations between dietary FA intakes and FAC of plasma TG and erythrocytes by introducing potential confounders such as age, body mass index (BMI), presence of diabetes mellitus, and total fat intake. One-way analysis of variance was used to compare total ω-3 PUFA, EPA, and DHA in plasma TG and erythrocytes across tertiles of daily fish and shellfish consumption, with Bonferroni post hoc testing for pairwise comparisons. All analyses were computed using the SPSS version 26 (IBM, Chicago, IL, USA). Statistical significance was set at $P < 0.05$ for all evaluated parameters.

Results

The final analysis included 333 patients (Fig. 1), whose characteristics are shown in Table 1. This population was multiethnic with Chinese (54.1%), Malay (29.4%), Indian (15.6%), and other races (0.95%), with mean age of 55 ± 14 y, and was composed of 54.4% men. The median of dialysis duration was 64 mo.

As shown in Table 2, the mean daily energy intake was significantly higher in men, reflecting significantly higher consumption of protein, total fat, MUFAs, and PUFAs. Quantitative consumption of carbohydrates, SFA, and trans fat and the percent energy intake contributed by all macronutrients were not significantly different for men and women ($P > 0.05$). The main dietary FA intakes were SFAs (12.2%) and MUFAs (11.9%). Dietary palm oil usage was reported in 93.4% participants, whereas only 2.1% reported taking fish oil supplements.

In relation to individual FA distribution reported as percentage FAC (Table 3), the most abundant FAs identified in both diet and plasma TG was OA (41.56 ± 3.02%) followed by PA (29.13 ± 2.55%) and LA (14.53 ± 2.51%). On the contrary, the highest proportion of FAs in erythrocytes was PA (24.79 ± 2.75%) followed by SA (19.94 ± 2.15%), OA (17.51 ± 2.86%), and AA (11.61 ± 2.54%).

The associations between dietary FA intakes and the respective FA of plasma TG and erythrocyte are shown in Table 4. The correlation coefficients were consistent even after adjustments for potential confounders. Dietary total PUFAs, ω-6 PUFAs, and ω-3 PUFAs were significantly correlated to plasma TG, with DHA having the strongest correlation, followed by LA and ALA. There was no

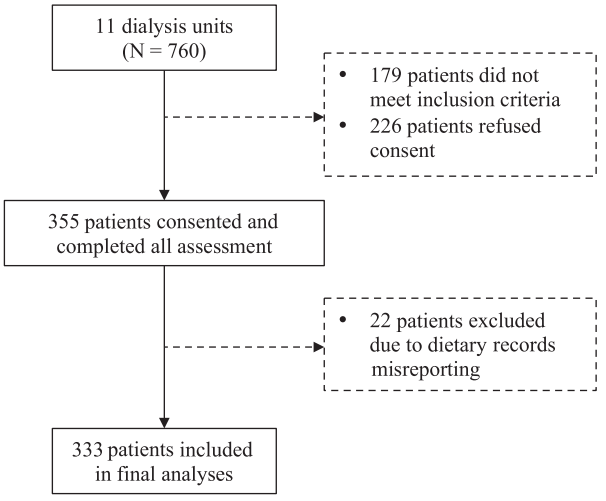

Fig. 1. Flow chart of patient enrollment and analysis in this study.

significant association between dietary total SFAs, MUFAs or trans fat with plasma TG. Nevertheless, dietary trans-18:2 ω-6 isomers were significantly associated with plasma TG. In terms of erythrocyte FA, significant associations were only observed between dietary and erythrocytes FAs for total ω-3 PUFA and DHA. An additional observation was that participants in tertile 3 of daily fish and shellfish consumption compared with those in tertile 1 (0.69 ± 0.45% versus 0.53 ± 0.42%, $P = 0.023$) had significantly greater plasma TG DHA (Fig. 2). For association between dietary FA and plasma TG FA (Table 5), dietary total SFA, lauric acid, myristic acid, and PA were directly associated with plasma TG MUFA and OA, whereas they were inversely associated with plasma TG total PUFAs, ω-3 PUFAs, and ω-6 PUFAs. On the other hand, dietary total PUFAs, ω-3 PUFAs, ω-6 PUFAs, LA, and ALA were inversely associated with plasma TG MUFA and OA. For association between dietary FA and erythrocyte FA (Table 6), dietary AA, ω-3 PUFA, EPA, and DHA were inversely associated with erythrocyte MUFA, whereas dietary PA and OA were directly associated.

Table 1
Patient baseline characteristics (N = 333)

	Mean ± SD/n (%)
Age (y)	54.9 ± 13.9
Sex	
Male	181 (54.4)
Female	152 (45.6)
Ethnicity	
Malay	98 (29.4)
Chinese	180 (54.1)
Indian	52 (15.6)
Others	3 (0.9)
Dialysis vintage (mo)	64 (81)*
Comorbidities	
Diabetes mellitus	134 (40.2)
Hypertension	262 (78.7)
Dry weight (kg)	61 ± 14
Height (cm)	158± 8.7
Body mass index (kg/m^2)	24.3 ± 4.83
Predialysis urea (mmol/L)	19.7 ± 5.38
Predialysis creatinine (μmol/L)	827.4 ± 206.7
Serum phosphorus (mmol/L)	1.78 ± 0.51
Albumin (g/L)	39.0 ± 3.99
Hemoglobin (g/L)	10.7 ± 1.71
Kt/V	1.67 ± 0.41

*Median (interquartile range) as data was skewed to the right.

Table 2
Daily dietary intakes (mean ± SD) assessed using 3-d diet records

	All (N = 333)	Men (n = 181)	Women (n = 152)	*P*-value*
Energy (kcal)	1574 ± 374	1715 ± 369	1407 ± 304	**0.036**
Energy (kcal/kg IBW)	25.2 ± 5.6	25.9 ± 5.8	24.3 ± 5.2	**0.007**
Protein (g)	57.5 ± 20.4	63.1 ± 22.1	50.8 ± 15.7	**0.001**
Protein (g/kg IBW)	0.92 ± 0.30	0.95 ± 0.32	0.88 ± 0.27	**0.030**
Protein (% EN)	14.6 ± 3.5	14.7 ± 3.8	14.5 ± 3	0.247
Carbohydrate (g)	222.8 ± 54.5	241 ± 54.4	201.1 ± 46.4	0.111
Carbohydrate (% EN)	57.0 ± 7.7	56.6 ± 8.2	57.4 ± 7	0.075
Total fat (g)	50.3 ± 18.3	55.2 ± 19.5	44.3 ± 14.8	**0.040**
Total fat (% EN)	28.4 ± 6.2	28.6 ± 6.3	28.1 ± 6.1	0.996
SFA (g)	21.6 ± 8.2	23.8 ± 8.6	19.1 ± 6.9	0.051
SFA (% EN)	12.2 ± 2.9	12.3 ± 2.9	12.1 ± 3	0.774
MUFA (g)	21 ± 7.9	23.0 ± 8.4	18.6 ± 6.4	**0.024**
MUFA (% EN)	11.9 ± 2.9	11.9 ± 2.9	11.8 ± 2.8	0.533
PUFA (g)	7.5 ± 3.4	8.3 ± 3.7	6.6 ± 2.7	**0.006**
PUFA (% EN)	4.2 ± 1.5	4.3 ± 1.5	4.2 ± 1.4	0.761
Trans fat (g)	0.10 ± 0.08	0.10 ± 0.09	0.09 ± 0.07	0.088
Trans fat (% EN)	0.05 ± 0.04	0.05 ± 0.04	0.06 ± 0.05	0.726
Cooking oil*				
Palm oil	311 (93.4)	170 (93.6)	141 (92.8)	0.671†
Other oils	22 (6.6)	11 (6.1)	11 (7.2)	
Fish oil supplements*				
Yes	7 (2.1)	2 (1.1)	5 (3.3)	0.253‡
No	326 (97.9)	179 (98.9)	147 (96.7)	

EN, energy; IBW, ideal body weight; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.
Values in **bold** indicate *P*-value <0.05. *n (percentage)
*Independent *t* test.
†Pearson's χ^2 test.
‡Fisher's exact test.

Table 3
Percent FAC of individual FAs and FA classes of dietary, plasma TG, and erythrocytes

	Percent FAC (%)		
Fatty acid* profile	Dietary	Plasma TG	Erythrocytes
SFA			
12:0	2.64 ± 3.12	0.88 ± 1.19	0.82 ± 0.80
14:0	2.16 ± 1.62	1.33 ± 0.59	1.68 ± 0.81
16:0	31.30 ± 3.21	29.13 ± 2.55	24.79 ± 2.75
18:0	5.64 ± 1.50	3.58 ± 0.81	19.94 ± 2.15
Total	43.20 ± 5.12	35.51 ± 3.14	50.45 ± 4.41
MUFA			
16:1 ω-7	1.35 ± 0.70	3.06 ± 1.11	0.75 ± 0.65
18:1	39.96 ± 3.63	41.56 ± 3.02	17.51 ± 2.86
Total	41.88 ± 3.71	45.19 ± 3.26	21.74 ± 3.21
PUFA			
ω-6 PUFA			
18:2 ω-6	13.27 ± 3.05	14.53 ± 2.51	7.52 ± 1.53
20:4 ω-6	0.12 ± 0.14	0.96 ± 0.41	11.61 ± 2.54
Total	13.90 ± 3.35	15.82 ± 2.60	20.46 ± 3.16
ω-3 PUFA			
18:3 ω-3	0.53 ± 0.41	0.57 ± 0.56	0.41 ± 0.38
20:5 ω-3	0.12 ± 0.18	0.23 ± 0.24	0.64 ± 0.44
22:6 ω-3	0.23 ± 0.48	0.59 ± 0.43	3.02 ± 1.15
Total	0.92 ± 0.76	0.99 ± 0.81	4.02 ± 1.86
Total PUFA	14.93 ± 3.67	16.96 ± 2.93	24.83 ± 4.36
Trans fat			
t-16:1 ω-7	0.04 ± 0.04	0.26 ± 0.12	0.71 ± 0.31
Trans-18:1 isomers	0.07 ± 0.12	0.19 ± 0.16	0.44 ± 0.28
Trans-18:2 isomers	0.08 ± 0.08	0.26 ± 0.28	0.50 ± 0.27
Total	0.19 ± 0.16	0.29 ± 0.26	1.04 ± 0.57

3-DDR, 3-d dietary records; FAC, fatty acid composition; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TG, triacylglycerol.
*Values presented as mean ± SD.
*Fatty acid abbreviations: 12:0, lauric acid; 14:0, myristic acid; 16:0, palmitic acid; 16:1 ω-7, palmitoleic acid; *t*-16:1 n7, trans-9–hexadecenoic acid; 18:0, stearic acid; 18:1 ω-9, oleic acid; 18:2 ω-6, linoleic acid; 18:3 ω-3, α-linolenic acid; 20:4 ω-6, arachidonic acid; 20:5 ω-3, eicosapentaenoic acid; 22:4 ω-6, adrenic acid; 22:5 ω-3, docosapentaenoic acid; 22:6 ω-3, docosahexaenoic acid.

Discussion

In the present study, consumption of diets rich in SFAs (>10% of total calories) and MUFAs (>10% of total calories) but low in PUFAs (<5% of total calories) were observed in Malaysian patients undergoing HD. This finding is not unexpected because palm oil, which contains primarily SFAs (~45%) and MUFAs (~39%) [23], is the predominant cooking oil consumed in this HD population (~93%). Currently, there is no consensus in nutritional guidelines regarding optimal dietary FA intake for this group of patients [15,24]. For individuals without chronic kidney disease (CKD), the American Heart Association recommends reducing dietary SFA from 7% to about 5% or 6% of total calories and replacing SFAs with MUFAs (>20% of total calories) and PUFAs (>10% of total calories) to optimize the lowering of low-density lipoprotein cholesterol levels, as a means to reduce risk for CVD [25]. Limited adherence to this dietary FA recommendation was observed in our HD population as well as in patients on HD from the United States [26] and Spain [27]. Nevertheless, higher low-density lipoprotein cholesterol is paradoxically associated with better survival in patients undergoing HD [28]. Therefore, future research examining the relationship between dietary FA intake and clinical outcomes in patients undergoing HD is warranted to put forward recommendations for optimal dietary FA intake in this population.

Another major finding was that the dietary marine ω-3 PUFA intake in the HD population was noted to be below the optimal consumption level of 250 mg/d [29], which was also reflected in very low levels of erythrocyte ω-3 PUFA content, along with high SFA and MUFA erythrocyte content compared with their counterparts in other countries [8]. Harris [30] has proposed that the percentage of <4%, 4% to 8%, and >8% of erythrocyte ω-3 index (i.e., EPA + DHA), may denote high, intermediate, and low risk for CVD, respectively. Therefore, for our HD population, the mean erythrocyte ω-3 index <4% indicated high risk for CVD. The beneficial

Table 4
Associations between dietary fatty acids (% total dietary fat) and FAC of plasma TG and erythrocytes

Fatty acid* profile	Plasma TG		Erythrocytes	
	ρ (*P*-value)	Adjusted ρ (*P*-value)	ρ (*P*-value)	Adjusted ρ (*P*-value)
SFA				
12:0	0.059 (0.316)	0.054 (0.361)	0.080 (0.174)	0.043 (0.464)
14:0	0.138 (**0.013**)	0.108 (0.056)	−0.039 (0.489)	0.014 (0.808)
16:0	0.078 (0.163)	0.057 (0.311)	0.056 (0.319)	0.059 (0.294)
18:0	0.087 (0.122)	0.103 (0.066)	0.045 (0.422)	0.097 (0.084)
Total	0.086 (0.124)	0.006 (0.914)	0.046 (0.414)	0.074 (0.190)
MUFA				
16:1 ω-7	−0.072 (0.200)	−0.062 (0.274)	−0.078 (0.163)	−0.085 (0.131)
18:1	0.013 (0.823)	−0.044 (0.435)	0.021 (0.703)	0.063 (0.262)
Total	−0.032 (0.570)	−0.062 (0.274)	0.061 (0.273)	0.100 (0.076)
PUFA				
ω-6 PUFA				
8:2 ω-6	0.203 (<**0.001**)	0.162 (**0.004**)	0.073 (0.195)	0.024 (0.665)
20:4 ω-6	−0.101 (0.077)	−0.020 (0.724)	−0.023 (0.687)	0.032 (0.573)
Total	0.225 (<**0.001**)	0.222 (<**0.001**)	0.064 (0.251)	0.036 (0.529)
ω-3 PUFA				
18:3 ω-3	0.209 (<**0.001**)	0.148 (**0.014**)	−0.077 (0.451)	−0.062 (0.549)
20:5 ω-3	−0.057 (0.584)	−0.060 (0.570)	0.091 (0.204)	0.110 (0.127)
22:6 ω-3	0.185 (**0.005**)	0.192 (**0.004**)	0.121 (**0.034**)	0.189 (**0.001**)
Total	0.133 (**0.017**)	0.115 (**0.040**)	0.173 (**0.002**)	0.178 (**0.002**)
Total PUFA	0.256 (<**0.001**)	0.251 (<**0.001**)	0.069 (0.218)	0.072 (0.202)
Trans fat				
t-16:1 ω-7	0.039 (0.575)	0.025 (0.730)	−0.079 (0.325)	−0.028 (0.729)
Trans-18:1 isomers	0.075 (0.334)	0.074 (0.350)	−0.033 (0.694)	−0.023 (0.792)
Trans-18:2 isomers	0.327 (**0.045**)	0.403 (**0.018**)	−0.027 (0.685)	−0.064 (0.336)
Total	0.083 (0.136)	0.108 (0.054)	0.004 (0.948)	−0.008 (0.898)

FAC, fatty acid composition; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acid; TG, triacylglycerol.
Values in **bold** indicate *P*-value <0.05.
*Fatty acid abbreviation: 12:0, lauric acid; 14:0, myristic acid; 16:0, palmitic acid; 16:1 ω-7, palmitoleic acid; *t*-16:1 ω-7, trans-9−hexadecenoic acid; 18:0, stearic acid; 18:1 ω-9, oleic acid; 18:2 ω-6, linoleic acid; 18:3 ω-3, α-linolenic acid; 20:4*n*ω-6, arachidonic acid; 20:5 ω-3, eicosapentaenoic acid; 22:4 ω-6, adrenic acid; 22:5 ω-3, docosapentaenoic acid; 22:6 ω-3, docosahexaenoic acid.

effects of circulating ω-3 PUFAs associated with clinical outcomes in patients on HD is already well established [8]; therefore, efforts should be made to optimize dietary ω-3 PUFA intakes in this high-risk HD population.

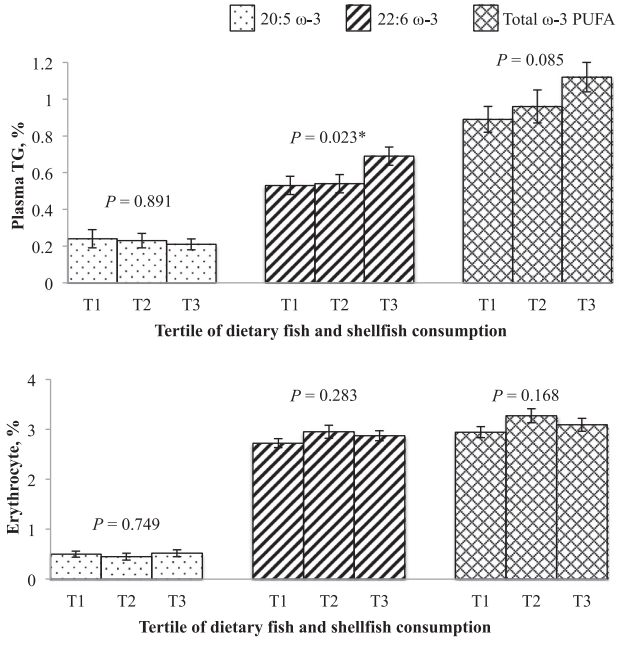

Fig. 2. Comparisons of mean plasma TG and erythrocyte 20:5 ω-3, 22:6 ω-3, and total ω-3 PUFA proportions based on tertile distributions of fish and shellfish consumption. *Bonferoni post hoc analysis for pairwise comparison of T1 vs T3, *P* = 0.037. PUFA, polyunsaturated fatty acid; T, tertile; TG, triacylglycerol.

We observed significant correlations between FA assessed by the 3-DDR method and the respective FA in plasma TG for total PUFAs, total ω-3 PUFAs, and total ω-6 PUFA composition and individual FAs such as LA, ALA, DHA, and trans-18:2 isomers. On the other hand, only significant correlations were shown between dietary and erythrocyte total ω-3 PUFAs and DHA. Comparison of our results with cited studies in dialysis populations is not possible at this time because dietary assessment with FA biomarkers has not been investigated [5–7]. However, in patients in the early stages of CKD, Huang et al. [31] observed strong correlations of dietary EPA, DHA, PA, and LA using 7-d food records, with FAs in cholesterol esters and adipose tissue.

Blood FA status reflects both exogenous FA of diet origins and endogenous *de novo* lipogenesis. SFAs such as myristic acid, PA, and SA can be synthesized endogenously via polymerization and elongation of acetyl-coenzyme A [32]. Stearoyl-coenzyme A desaturase (SCD-1) is a key enzyme involved in endogenous synthesis of MUFAs. SCD-1 catalyzes the introduction of a *cis*-double bond in the ω-9 position, therefore converting SA into OA and PA into palmitoleic acid [33]. Because SFAs and MUFAs in plasma TG and erythrocytes can be synthesized endogenously, the circulating concentrations may be beyond dietary influence [34]. SCD-1 is modulated by dietary factors, such as dietary carbohydrate and SFA enhancing the activity of SCD-1, whereas dietary PUFAs diminish the action of SCD-1 [35]. Therefore, positive associations between dietary SFAs and plasma MUFAs, and inverse associations between dietary PUFAs and MUFAs were observed in this study, suggesting potential modulations of SCD-1 activity by dietary FAs.

In the PUFA synthetic pathway, δ-12-desaturase catalyzes the synthesis of LA from OA and δ-15-desaturase converts LA to ALA. However, humans lack these two enzymes to synthesize LA and ALA endogenously, and these essential FAs must be consumed

Table 5
Associations between dietary FA* intake (% total dietary fat) and plasma TG FAs

		Plasma TG FA (%)															
		SFA	12:0	14:0	16:0	18:0	MUFA	16:1 ω-7	18:1	PUFA	ω-6 PUFA	18:2 ω-6	20:4 ω-6	ω-3 PUFA	18:3 ω-3	20:5 ω-3	22:6 ω-3
Dietary FA (% total fat)	SFA	0.006	0.064	0.088	−0.004	−0.072	**0.222**†	0.091	**0.200**†	**−0.255**†	**−0.240**†	**−0.243**†	−0.034	**−0.144**‡	−0.072	0.001	−0.090
	12:0	0.051	0.054	**0.136**‡	0.056	**−0.127**‡	**0.122**‡	0.103	0.105	**−0.159**†	**−0.147**†	**−0.157**†	0.029	−0.079	−0.061	0.029	0.032
	14:0	0.004	0.062	0.108	−0.019	−0.069	**0.179**†	0.068	0.166	**−0.172**†	**−0.175**†	**−0.188**†	0.018	−0.053	0.013	0.058	−0.041
	16:0	0.015	−0.033	−0.016	0.057	−0.029	**0.131**‡	0.045	**0.114**‡	**−0.187**†	**−0.165**†	**−0.139**‡	**−0.130**‡	**−0.151**†	**−0.136**‡	−0.025	−0.067
	18:0	−0.080	0.055	−0.091	−0.128	0.103	−0.047	−0.038	−0.046	0.085	0.081	0.069	0.038	0.024	0.056	−0.075	−0.117
	MUFA	−0.040	−0.047	**−0.142**‡	−0.020	0.038	−0.062	−0.048	−0.044	0.104	**0.112**‡	**0.125**‡	−0.032	0.008	−0.004	−0.163	−0.088
	16:1 ω-7	0.033	−0.028	−0.009	0.044	0.049	−0.037	−0.069	−0.009	0.009	−0.010	−0.002	−0.003	0.062	0.102	0.165	−0.049
	18:1	−0.040	−0.042	**−0.139**‡	−0.019	0.023	−0.055	−0.028	−0.044	0.100	**0.113**‡	**0.124**‡	−0.030	−0.010	−0.027	−0.194	−0.080
	PUFA	0.032	−0.042	0.020	0.025	0.062	**−0.247**†	−0.078	**−0.234**†	**0.251**†	**0.223**†	0.213	0.080	**0.193**†	0.104	0.166	**0.195**†
	ω-6 PUFA	0.034	−0.038	0.032	0.023	0.063	**−0.232**†	−0.061	**−0.222**†	**0.248**†	**0.222**†	**0.205**†	0.087	**0.183**†	0.107	0.187	**0.165**†
	18:2 ω-6	0.059	−0.023	0.039	0.045	0.059	**−0.203**†	−0.072	**−0.180**‡	**0.190**†	**0.166**†	**0.162**†	0.048	**0.161**†	0.097	0.176	**0.158**‡
	20:4 ω-6	−0.028	−0.088	−0.058	−0.001	0.029	**−0.116**‡	−0.071	**−0.121**†	0.059	0.031	0.046	−0.020	0.109	0.014	−0.039	**0.133**†
	ω-3 PUFA	−0.001	−0.039	−0.052	0.023	0.014	**−0.158**†	−0.104	**−0.114**‡	**0.116**‡	0.097	**0.119**‡	0.005	**0.115**‡	0.027	0.002	**0.119**†
	18:3 ω-3	−0.035	−0.016	−0.099	−0.033	0.058	**−0.164**†	−0.146	−0.113	0.185	**0.186**†	**0.191**†	0.046	0.077	**0.148**‡	0.139	0.020
	20:5 ω-3	0.013	−0.051	0.020	0.037	−0.008	−0.062	−0.010	−0.083	0.035	0.005	0.023	−0.020	**0.111**‡	−0.044	−0.060	**0.247**†
	22:6 ω-3	0.028	−0.031	0.007	0.054	−0.024	−0.081	−0.031	−0.096	0.014	−0.005	0.016	−0.017	0.072	−0.052	−0.049	**0.192**†
	EFA	0.049	−0.023	0.024	0.037	0.062	**−0.206**†	−0.083	**−0.178**†	**0.197**†	**0.174**†	**0.172**†	0.050	**0.157**†	0.107	0.179	**0.148**‡

EFA, essential fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acid; TG, triacylglycerol.
Values in **bold** indicate *P*-value <0.05.
*Fatty acid abbreviations: 12:0, lauric acid; 14:0, myristic acid; 16:0, palmitic acid; 16:1 ω-7, palmitoleic acid; *t*-16:1 ω-7, trans-9−hexadecenoic acid; 18:0, stearic acid; 18:1 ω-9, oleic acid; 18:2 ω-6, linoleic acid; 18:3 ω-3, α-linolenic acid; 20:4 ω-6, arachidonic acid; 20:5 ω-3, eicosapentaenoic acid; 22:4 ω-6, adrenic acid; 22:5 ω-3, docosapentaenoic acid; 22:6 ω-3, docosahexaenoic acid.
†$P < 0.01$.
‡$P < 0.05$.

Table 6
Associations between dietary FA* intake (% total dietary fat) and erythrocyte FAs

		Erythrocytes FA (%)															
		SFA	12:0	14:0	16:0	18:0	MUFA	16:1 ω-7	18:1	PUFA	ω-6 PUFA	18:2 ω-6	20:4 ω-6	ω-3 PUFA	18:3 ω-3	20:5 ω-3	22:6 ω-3
Dietary FA (% total fat)	SFA	0.074	0.019	−0.034	0.110	0.001	−0.037	−0.022	−0.002	−0.053	−0.065	−0.069	−0.050	−0.041	0.120	−0.023	−0.059
	12:0	0.078	0.043	−0.001	0.103	0.009	−0.086	−0.037	−0.035	−0.033	−0.043	−0.099	−0.018	−0.019	0.092	−0.045	−0.012
	14:0	**0.121**†	0.071	0.014	0.082	0.067	−0.106	−0.032	−0.056	−0.082	−0.103	**−0.120**†	−0.074	−0.062	0.104	−0.014	−0.079
	16:0	−0.042	−0.064	−0.032	−0.059	**−0.120**†	**0.121**†	0.034	0.108	−0.020	−0.005	0.063	−0.016	−0.020	0.074	−0.019	−0.013
	18:0	0.019	0.013	−0.021	−0.034	0.097	−0.046	0.006	−0.088	0.044	0.033	0.014	0.022	0.037	−0.059	0.057	−0.010
	MUFA	−0.042	−0.014	0.050	−0.042	−0.040	0.100	0.048	0.047	0.016	0.039	0.082	0.035	0.023	−0.060	0.042	0.008
	16:1 ω-7	0.002	0.034	0.049	−0.009	0.009	−0.077	−0.086	−0.044	0.015	0.008	0.005	0.012	0.057	0.002	0.017	0.049
	18:1	−0.043	−0.015	0.041	−0.039	−0.049	**0.123**†	0.061	0.063	0.007	0.034	0.079	0.031	0.007	−0.060	0.040	−0.007
	PUFA	−0.060	−0.013	−0.004	−0.110	0.039	−0.050	−0.018	−0.045	0.058	0.051	0.014	0.033	0.034	−0.104	−0.011	0.074
	ω-6 PUFA	−0.052	−0.011	−0.008	**−0.112**†	0.052	−0.024	−0.002	−0.024	0.034	0.036	0.007	0.022	0.005	−0.088	−0.016	0.041
	18:2 ω-6	−0.085	−0.006	−0.005	**−0.125**†	0.004	−0.005	0.009	−0.007	0.055	0.056	0.025	0.039	0.019	−0.080	−0.033	0.060
	20:4 ω-6	−0.014	0.083	0.052	−0.021	−0.054	**−0.127**†	−0.096	−0.101	0.083	0.060	0.037	0.032	0.107	−0.072	0.039	0.121†
	ω-3 PUFA	−0.049	−0.012	0.022	−0.030	−0.038	**−0.127**†	−0.075	−0.108	**0.119**†	0.084	0.029	0.066	**0.130**†	−0.108	0.004	**0.163**‡
	18:3 ω-3	−0.072	−0.063	−0.044	−0.085	0.046	0.012	−0.066	−0.009	0.082	**0.120**†	0.054	0.094	−0.055	−0.063	**−0.155**†	−0.021
	20:5 ω-3	−0.009	0.032	0.047	0.012	−0.066	**−0.138**†	−0.066	−0.091	0.075	0.017	0.005	0.011	**0.164**‡	−0.091	0.110	**0.181**‡
	22:6 ω-3	−0.011	0.018	0.041	0.020	−0.069	**−0.151**‡	−0.052	**−0.117**†	0.081	0.019	−0.010	0.017	**0.175**‡	−0.087	0.090	**0.189**‡
	EFA	−0.086	−0.013	−0.010	**−0.125**†	0.010	−0.003	0	−0.008	0.060	0.066	0.029	0.047	0.010	−0.081	−0.050	0.052

EFA, essential fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acid.
Values in **bold** indicate. *P*-value <0.05.
*Fatty acid abbreviations: 12:0, lauric acid; 14:0, myristic acid; 16:0, palmitic acid; 16:1 ω-7, palmitoleic acid; *t*-16:1 ω-7, trans-9−hexadecenoic acid; 18:0, stearic acid; 18:1 ω*n*-9, oleic acid; 18:2 ω-6, linoleic acid; 18:3 ω-3, α-linolenic acid; 20:4 ω-6, arachidonic acid; 20:5 ω-3, eicosapentaenoic acid; 22:4 ω-6, adrenic acid; 22:5 ω-3, docosapentaenoic acid; 22:6 ω-3, docosahexaenoic acid.
†$P < 0.05$.
‡$P < 0.01$.

from the diet [36]. Therefore, LA and ALA, and detrimental TFAs [37] that also cannot be produced endogenously, are likely to demonstrate strong associations with dietary exposure. ALA is potentially a substrate to synthesize EPA and DHA, but the conversions are relatively inefficient in humans [38]. Therefore, both EPA and DHA levels in the present HD population were more likely attributed to direct dietary exposure from fish consumption. In fact, it was shown that low plasma and erythrocyte ω-3 PUFA levels of 75 US patients on HD probably could be attributed to low average weekly fish servings [39]. The present study corroborated that greater fish consumption in our patients, measured in absolute weight in grams, was associated with higher plasma TG DHA concentrations (Fig. 2). An unanticipated finding was the lack of association of dietary EPA with both plasma TG and erythrocytes, which has not been observed in other non-dialysis populations. It is hypothesized that the ω-3 PUFA elongation pathway in patients on HD may be affected by the uremic milieu [39].

Compared with healthy controls, patients on HD have been reported to have higher circulating MUFA and OA levels [8], and Son et al. [40] showed that erythrocyte MUFAs and OA were associated with the vascular calcification score assessed by plain radiographic film, an independent predictor of CVD mortality in this group of patients. The inverse associations between dietary PUFAs and MUFAs assessed in plasma TG and erythrocyte lend credence that abnormalities of the blood FA profiles could be attributed to essential FA deficiency and enhanced activity of SCD-1 owing to inadequate PUFA intake. It has been hypothesized that more MUFAs may be produced to substitute the function of maintaining membrane fluidity during essential FA deficiency [41].

The choice of using the 3-DDR to assess dietary exposure instead of an FFQ was due to the lack of a validated FFQ tool applicable to Malaysian patients on dialysis. Designing and creation of a new dialysis FFQ for specific populations is challenging and requires substantial effort [42]. In addition, the dialysis FFQ is prone to underestimating energy and macronutrient intakes compared with the 3-DDR [43]. Still, the 3-DDR, after correction for misreporting, remains a valid tool in some studies assessing dietary FA intakes in HD populations [44,45].

An observation from this study was that the patients' daily dietary energy intakes were lower than the recommended 30 to 35 kcal/kg as per nutritional guidelines for patients with CKD [15,24]. Another Malaysian study (N = 205) also noted mean daily dietary energy intake of patients on HD as 23 kcal/kg [46]. This is not unusual as many other studies on HD populations also concur most patients are unable to optimize their energy requirements [47]. The suboptimal dietary intake in this patient population is often attributed to loss of appetite [47].

A major strength of this study was its use of a dietary FA database of local foods, developed by our own laboratory, which also carried out all FA analyses of plasma TG and erythrocytes required for this study. Thus, we have avoided interlaboratory variations in protocol and instrumentation. Second, FAC information from diet and two types of biological specimens were generated for each patient.

This study also had some limitations apart from its cross-sectional design. First, the findings may apply only to patients on dialysis and therefore potential extrapolation to other patients with CKD remains unknown. We also did not distinguish the type of fish consumption when examining the associations with plasma TG and erythrocyte ω-3 PUFAs.

The implication from this study is that suboptimal dietary intake of PUFAs, particularly ω-3 PUFAs, is evident for this population. This deficiency is also reflected in the plasma TG and erythrocyte FA status. It appears that patients who consume greater amounts of fish are able to achieve higher ω-3 PUFA status in plasma TG, although incorporation into erythrocytes remains vulnerable to uremia. With relevance to clinical practice, dietitians and nephrologists should emphasize the importance of adequate ω-3 PUFA consumption in patients on HD. Second, because FAs in plasma TG and erythrocyte reflected both exogenous (dietary) and endogenous origins, this study provides data on the dietary influence on circulating FA metabolism in patients on HD, which suggests a potential ability to modulate dietary fat to favorably alter the blood FA profile. Findings from this study also indicate that specific FA in plasma TG and erythrocyte could be used as an objective biomarker to assess the quality of FA intakes in epidemiologic studies and compliance in intervention studies. The results of this study can be used as the baseline data for potential future prospective follow-up studies to evaluate clinical outcomes associated with dietary and circulating FA in patients on HD.

Conclusion

SFAs and MUFAs were the predominant FAs consumed in this Malaysian HD population, concomitant with suboptimal intake of PUFAs, particularly the ω-3 PUFAs. The FA status of plasma TG and erythrocyte also reflected the dietary FA pattern. There were significant associations between FAs assessed by the 3-DDR and circulating FAs in plasma and erythrocytes, pertaining to ω-3 and ω-6 PUFAs. Therefore, plasma and erythrocyte FAs adequately reflected recent dietary PUFA exposure and can be used as a biomarker to assess these FA intakes in patients on HD. Elevated plasma TG MUFAs may be due to deficiencies in PUFA intakes. The lack of association between plasma and erythrocyte EPA with dietary exposure may suggest altered FA metabolism in the uremic state.

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