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Original Article

Hypercholesterolemia as the first manifestation of metabolic abnormalities in normoglycemic young adult male with family history of type 2 diabetes mellitus

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ABSTRACT

Background: Although several studies reported high number of metabolic disorder among First Degree Relatives (FDR) of Type 2 Diabetes Mellitus (T2DM), only a few studies analyzed the impact of gender on the occurence of metabolic abnormalities.
Aims: This study aimed to investigate the first manifestation of metabolic abnormalities in normoglycemic FDR of T2DM.
Methods and materials: This cross-sectional study recruited 60 FDR of T2DM age of 19–39 years old in Jakarta, Indonesia. We matched 60 non-FDR as controls. All participants had neither glucose intolerance nor hypertension. Anthropometry, body composition and laboratory measurements (blood glucose, HbA1c, lipid profile, liver and kidney function test) were assessed.
Results: In males, FDR aged 30–39 years old had higher Total Cholesterol (TC) level ([233 ± 51.43 mg/dL vs. 177.83 ± 22.08 mg/dL, p = 0.036] and Low Density Lipoprotein Cholesterol (LDL-C) level [173.83 ± 39.83 mg/dL vs. 125.67 ± 21.50 mg/dL, p = 0.026] than those of non-FDR significantly. FDR also had higher risk of hypercholesterolemia than non-FDR [OR 5.25 (1.09–25.21)]. There were no differences of metabolic abnormalities between female FDR and non-FDR group.
Conclusion: Male FDR of T2DM showed higher level of TC and LDL-C level than those of non FDR. Male FDR also showed higher risk of dyslipidemia.

1. Introduction

Diabetes Mellitus (DM) is a major health problem worldwide. The global prevalence of DM increased according to World Health Organization (WHO) data in 2014. As many 442 million adults had diabetes, which four time higher than in 1980 [1]. For the past 7 years, the prevalence of DM had increased in Indonesia. According to RISKESDAS (Indonesian Basic Health Research), an estimated 5.7% of adults in 2007 had DM compared to 6.9% in 2013 [2]. The incidence of DM was increased due to genetic and environmental factors. While the mechanisms behind genetic factors have not been well established, environmental factors like physical inactivity, diet, smoking, alcohol consumption and obesity were believed to contribute to blood glucose homeostasis [3,4].

People with FDR of T2DM are significantly associated with higher incidence of DM in the future. Several studies had reported many metabolic disorder found in FDR. A study by *Amini* et al. in Iran found nearly 50% of FDR subjects had abnormal glucose levels consisting of Impaired Fasting Glucose/IFG (17.3%), Impaired Glucose Tolerance/IGT (19.5%) and T2DM (19.5%), which were higher than those in the general population based on International Diabetes Federation (IDF) data in 2006 [5]. A 7-year cohort study by *Sakurai* et al. in Japan showed that the incidence of T2DM in FDR group was higher than that in non-FDR group [1.84 (1.36–2.47)], despite similar baseline characteristics in both groups at the begining [6]. *Hilding* et al. in Sweden found that a male FDR group had higher chance of developing T2DM than a female FDR group [OR: 3.1 (1.7–5.6) vs OR: 1,7 (1.0–3.0)] [7].

Insulin resistance is a major predictor of the development of

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T2DM, hypertension, dyslipidemia and atherosclerotic disease [8]. *Purnamasari* et al. in Indonesia showed that as many 26.67% of the siblings of T2DM patients had insulin resistance (insulin resistance was defined by the highest percentile from of Homeostatic Model Assessment for Insulin Resistance/HOMA-IR) [9]. *Kumar* et al. in India supported the previous studies and reported that 37.8% of FDR of T2DM had insulin resistance and more than 50% of FDR of T2DM developed metabolic syndrome [10]. Metabolic syndrome, a clinical manifestasion of insulin resistance, was diagnosed based on National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III) criteria which consisted of at least 3 out of 5 criteria including hyperglycemia (Fasting Blood Glucose/FBG $\geq$ 100 mg/dL), hypertriglyceridemia (Triglycerides/TG $\geq$ 150 mg/dL or taking lipid lowering agents), low High Density Lipoprotein Cholesterol/HDL-C (HDL-C < 50 mg/dL for female and HDL-C <40 mg/dL for male or taking lipid lowering agents), hypertension (blood pressure $\geq$ 130/85 mmHg or taking hypertension drugs) and central obesity (Waist Circumference/WC, male $\geq$ 90 cm and female $\geq$ 80 cm) [11]. *Ogedengbe* et al. in Nigeria showed that the prevalence of metabolic syndrome in T2DM, FDR of T2DM and normoglycemic groups were 87.1%, 16.7% and 13.5% respectively [12]. *Siewert* et al. in Argentina showed a significantly higher prevalence of metabolic syndrome in FDR of T2DM compared to the control group (34.8% vs 20.5%, $p < 0.025$). People with metabolic syndrome have 5 times greater risk of developing T2DM than those without the metabolic syndrome [13].

Several studies regarding metabolic disorders in FDR of T2DM mostly recruited subjects older than 40 years old, who were naturally at risk for metabolic disorder even if there was no family history of metabolic disorder. To the best of our knowledge, there is no study regarding metabolic abnormalities in FDR of T2DM which involved only young adult population with normoglycemic and normotensive profile. This study aimed to determine the profile of glucose intolerance among FDR of T2DM compared to non-FDR, and the profile of metabolic abnormalities among normoglycemic FDR of T2DM. The results of this study were expected to provide an overview of early metabolic disorders among FDR of T2DM in the framework of diabetes prevention plan.

2. Material and methods

2.1. Study subjects

This was a cross-sectional study which recruited 178 subject, age of 19–39 years old, which consisted of 108 FDR T2DM and 70 non-FDR (included in first data collection and analysis). The FDR group was obtained from the offspring of T2DM patients who visited outpatient diabetes clinic at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The age-sex-matched control group was obtained from hospital employees who did not have a family history of T2DM. Subjects with chronic kidney disease, liver disorder, cardiovascular disorders, chronic gastrointestinal disease, autoimmune disorders, malignancy, long-term steroid users and pregnant or lactating women were excluded from this study.

As many as 120 out of 178 participants with normolygcemia and normotensive subjects, consisted of 60 FDR of T2DM and 60 age-sex-matched non-FDR, were willing to take part in further examinations (second data collection). The study participants were divided by gender (female and male) and then categorized into two age groups (19-<30 years and 30-<40 years). All the subject were examined and recorded in a performed data sheet, after being given an informed consent. This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (0242/UN2.F1/ETIK/2018).

2.2. Measurements and laboratory assays

All 178 subjects underwent first data collection including interview, anthropometric assessment (Body Mass Index/BMI), HbA1c and Random Blood Glucose (RBG) level measurements. BMI was calculated as weight (kg) divided by height (m^2). HbA1c and RBG examination were performed using A1c EZ 2.0 Glycohemoglobin Analyzer and Accu Check Performance tool respectively.

For second data collection participants who had HbA1c $\geq$ 5.7% or RBG > 200 mg/dL were excluded. Study participants with normoglycemia and normotensive (120 subject) underwent a second data collection, which consisted of a spesific anthropometric measurements (abdominal circumference, WC and Waist Hip Ratio/WHR), body composition assessment with Bioelectrical Impedance Analysis (BIA) and laboratory tests (FBG, TC, LDL-C, HDL-C and TG, Aspartate Transaminase/AST, Alanine Transaminase/ALT, Creatinine/Cr and Estimated Glomerular Filtration Rate/e-GFR).

2.3. Statistical analysis

Data was analyzed using SPSS version 20. In bivariate analysis, normally distributed data was analyzed using independent T-test and non-normally distributed data was analyzed using Mann-Whitney test. Subsequent analysis was carried out by grouping numerical data into categorical and using Chi-square test to get the odds ratio. A value of $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Results of first data colection

The study was conducted in two steps. In first steps, there were 178 study participants consisting of 108 FDR and 70 non-FDR, who underwent BMI, HbA1c and RBG examination. The proportion of IGT was higher in FDR of T2DM than that in non FDR group, which was statistically not significant (Table 1). Baseline characteristics of all subjects were listed in Table 1. The FDR group had higher BMI than the non-FDR group [23.25 (15.80–40.00) kg/m^2 vs 22.65(15.62–34.15) kg/m^2, $p = 0.034$]. By classifying BMI and HbA1c into categorical data, the FDR T2DM group had significantly higher risk of overweight and obesity compared to the non-FDR group [68% vs 32%, $p = 0.028$, OR 1.977 (95%CI 1.074–3.638)]. In addition, the FDR T2DM group had higher risk of IGT than non-FDR (78.3% vs 21.7%, $p = 0.064$, OR 2.60 (0.918–7.363)] although it was statistically insignificant.

3.2. Results of second data colection

In the second steps, we recruited subjects with Normal Glucose Tolerance (NGT) and had BMI less than 30 kg/m^2. As many as 120 study participants fullfilled the criteria. Subjects were classified based on sex and age (19-<30 years and 30-<40 years) for further analysis.

In female group, there were no statistical differences in BMI, WC), HbA1c, RBG, lipid profile, liver and kidney function results between the FDR of T2DM and the non-FDR groups (data not shown). Female FDR of T2DM aged 30–<40 years had higher lipid profile (TC, LDL-C and TG) than those aged 19–<30 years old. Similar results were also found in WC, WHR and visceral fat parameters. Baseline characteristics in female subjects were listed in Table 2.

Unlike the female group, there were several significant differences regarding metabolic disorders between the FDR of T2DM and

Table 1
Baseline characteristics of both groups.

Variable	FDR	Non-FDR	p-value	OR (CI 95%)
Height (m)	1.58 (1.45–1.84)	1.59 (1.44–1.77)	0.272	
Weight (kg)	63.04 (±14.79)	59.20 (±11.60)	0.069	
BMI (kg/m^2)	23.25 (15.80–40.00)	22.65 (15.62–34.15)	0.034[a]	
>=23	66 (68.0)	31 (32.0)	0.028[b]	1.977 (1.074–3.638)
<23	42 (51.9)	39 (48.1)		
RBG (mg/dL)	94.00 (72–327)	91.50 (66–138)	0.179	
A1c (%)	5.20 (3.9–11.3)	5.20 (4.0–6.1)	0.508	
>=5.7	18 (78.3)	5 (21.7)	0.064	2.60 (0.918–7.363)
<5.7	90 (58.1)	65 (41.9)		

[a] Mann-whitney.
[b] Chi-square.

Table 2
Baseline characteristics of female FDR of T2DM and non-FDR based on specific age group.

Variable	FDR	Non FDR	P	FDR	Non FDR	P
	19–<30 (n = 25)	19–<30 (n = 25)	19-<30	30–<40 (n = 18)	30–<40 (n = 18)	30-<40
RBG (mg/dL)	95.24 ± 17.50	94.12 ± 14.09	.969	93.0 (50–72)	91.5 (66–127.0)	.536
HbA1c (%)	4.94 ± .32	5.13 ± .37	.062	5.20 (4.50–5.50)	5.05 (4.50–5.60)	.919
FBG (mg/dL)	87.0 (69.0–104.0)	82.0 (75.0–111.0)	.893	81.61 ± 6.66	81.50 ± 8.58	.966
TC (mg/dL)	187.80 ± 34.47	184.64 ± 36.74	.755	192.00 ± 23.09	196.27 ± 32.00	.649
LDL-C (mg/dL)	121.80 ± 33.45	115.32 ± 34.88	.506	130.50 ± 28.09	138.61 ± 33.00	.433
HDL-C (mg/dL)	56.08 ± 11.29	55.44 ± 10.38	.836	54.33 ± 7.94	50.89 ± 10.15	.265
TG (mg/dL)	75.0 (40.0–233.0)	75.0 (38.0–185.0)	.627	82.28 ± 27.32	86.61 ± 31.05	.776
AST (U/L)	18.0 (12.0–25.0)	16.0 (13.0–71.0)	.675	18.00 ± 5.42	16.50 ± 3.57	.293
ALT (U/L)	17.0 (6.0–37.0)	15.0 (8.0–103.0)	.355	16.0 (10.0–62.0)	16.0 (9.0–44.0)	.589
Cr (mg/dL)	.70 (.50–.80)	.60 (.50–.80)	.858	.70 (.60–.80)	.60 (.50–.80)	.133
e-GFR (mL/min/1.73 m^2)	122.98 ± 7.71	123.1 ± 8.45	.949	113.3 ± 5.64	115.38 ± 9.05	.398
Weight (kg)	56.48 ± 9.80	53.83 ± 13.28	.426	51.45 (32.60–92.40)	55.85 (45.50–74.20)	.846
Height (m)	1.56 ± 0.04	1.58 ± 0.06	.290	1.53 ± .05	1.56 ± .04	.084
BMI (kg/m^2)	23.27 ± 3.99	21.71 ± 4.80	.219	22.94 (14.98–36.09)	22.70 (19.15–29.79)	.856
WC (cm)	76.33 ± 8.33	76.67 ± 10.28	.898	79.92 ± 11.98	82.32 ± 10.28	.522
Hip circumference (cm)	95.5 (39.0–112.0)	91.0 (80.5–123.5)	.983	94.95 ± 10.00	96.16 ± 6.90	.675
WHR	.79 ± .05	.76 ± .06	.140	.83 ± .05	.85 ± .05	.166
Fat (%)	34.96 ± 6.22	32.73 ± 8.00	.276	34.76 ± 7.58	34.48 ± 5.46	.900
Fat Mass (kg)	20.68 ± 7.52	18.51 ± 9.51	.375	18.20 (6.90–47.20)	18.35 (10.60–32.70)	.848
Free Fat Mass/FFM (kg)	36.00 ± 4.12	35.30 ± 4.35	.564	35.57 ± 4.64	36.83 ± 3.36	.357
Total Body Water/TBW (kg)	25.66 ± 3.29	24.65 ± 3.98	.332	24.90 (17.60–36.20)	25.90 (21.20–37.80)	.310
Lean Mass (kg)	34.26 ± 3.23	33.39 ± 3.96	.398	33.60 (30.50–42.60)	33.90 (29.0–41.60)	.919
Visceral fat	4.0 (1.0–12.0)	3.0 (1.0–15.0)	.189	5.0 (1.0–10.0)	5.0 (1.0–10.0)	.872
Sistole (mmHg)	102 (90–120)	100 (90–110)	.521	105 (88–124)	104 (90–120)	.621
Diastole (mmHg)	67 (60–80)	70 (50–72)	.510	70 (60–82)	69 (60–80)	.093

Data was displayed in mean(SD) or median(min-max).

non-FDR in males. The proportion of hypercholesterolemia was greater in the FDR group compared to non-FDR [75% vs 25%, p = 0.031, OR 5.25 (1.09–25.21)] (Table 3).

Further analysis found several differences in metabolic parameters between male FDR of T2DM and non-FDR when the data was analyzed based on specific age group distribution (19-<30 years and 30-<40 years). In the male group aged 19–30 years, there were no significant differences in BMI parameters, lipid profile, HbA1c, FBG and BIA examination between the FDR and non-FDR groups. However, male FDR of T2DM aged 30-<40 years showed higher proportion of hypercholesterolemia [233 ± 51.43 mg/dL vs. 177.83 ± 22.08 mg/dL, p = 0.036], increased level of LDL-C [173.83 ± 39.83 mg/dL vs. 125.67 ± 21.50 mg/dL, p = 0.026] and increased level of TG [151.33 ± 76.83 mg/dL vs. 118.00 ± 58.59 mg/dL, p = 0.418] than the non-FDR group (Table 4). Male FDR aged 30-<40 years also had higher BMI [25.65 ± 2.73 kg/m^2 vs. 23.65 ± 3.098 kg/m^2, p = 0.263] and visceral fat [10.5 (7.0–14.0) vs. 10.0 (4.0–12.0), p = 0.325] than the non-FDR group (Table 4).

Table 3
Metabolic profiles in male FDR of T2DM and non-FDR groups.

Variable	FDR (%)	Non FDR (%)	Pvalue*	OR (CI95%)
Male	n = 17	n = 17		
Hypercholesterolemia[a]	9 (75)	3 (25)	0.031	5.25 (1.09–25.21)
↑ LDL-C[b]	15 (53.6)	13 (46.4)	0.368	2.31 (0.36–14.72)
↓ HDL-C[c]	5 (55.6)	4 (44.4)	0.697	1.35 (0.29–6.26)
Hypertriglyceride[d]	4 (57.1)	3 (42.9)	0.671	1.44 (0.27–7.68)
IFG[e]	3 (75)	1 (25)	0.287	3.43 (0.32–36.83)
Central obesity[f]	3 (60%)	2 (40)	0.628	1.61 (0.23–11.09)
Overweight/obese[g]	9 (50)	9 (50)	1	1 (0.26–3.85)
↑ FFM**	10 (52.6)	9 (47.5)	0.730	1.27 (0.33–4.93)
↑ FM**	9 (50)	9 (50)	1	1 (0.26–3.85)

*Chi-square.
**High FFM/FM more than P_{50} based on subject cut-off.
[a] TC ≥ 200 mg/dL
[b] LDL ≥ 100 mg/dL
[c] HDL < 40 mg/dL
[d] TG ≥ 150 mg/dL
[e] FBG ≥ 100 mg/dL
[f] WC ≥ 90 cm
[g] BMI ≥ 23 kg/m^2

4. Discussion

To the best of our knowledge, this is the first Indonesian study

Table 4
Baseline characteristics of male FDR of T2DM and non FDR based on specific age group.

Variable	FDR	Non FDR	P	FDR	Non FDR	P
	19–<30 (n = 11)	19–<30 (n = 11)	19–<30	30–<40 (n = 6)	30–<40 (n = 6)	30–<40
RBG (mg/dL)	92.27 ± 12.95	96.36 ± 18.19	.550	98.33 ± 18.88	91.33 ± 11.48	.456
HbA1c (%)	5.02 ± .34	5.26 ± .25	.067	5.35 ± .104	5.35 ± .22	1.000
GDPFBG (mg/dL)	90.73 ± 8.25	88.27 ± 5.29	.416	84.33 ± 4.59	88.33 ± 4.41	.155
TC (mg/dL)	182.27 ± 37.72	183.72 ± 31.38	.923	233.00 ± 51.43	177.83 ± 22.08	.036*
LDL-C (mg/dL)	128.91 ± 39.59	130.90 ± 27.24	.892	173.83 ± 39.83	125.67 ± 21.50	.026*
HDL-C (mg/dL)	41.91 ± 6.33	46.45 ± 10.51	.233	44.33 ± 5.64	38.17 ± 7.03	.125
TG (mg/dL)	120.0 (51.0–233.0)	75.0 (46.0–146.0)	.094	151.33 ± 76.83	118.00 ± 58.59	.418
AST (U/L)	19.0 (15.0–39.0)	19.0 (13.0–44.0)	.947	21.50 ± 4.23	21.17 ± 5.91	.913
ALT (U/L)	16.0 (7.0–72.0)	21.0 (11.0–64.0)	.264	35.83 ± 26.79	34.50 ± 18.20	.922
Cr (mg/dL)	.90 (.70–1.00)	.90 (.90–1.20)	.109	.95 ± .105	.92 ± .075	.541
e-GFR (mL/min/1.73 m^2)	117.5 (76.30–130.20)	114.2 (83.0–122.5)	.374	108.3 (85.3–118.2)	109.5 (72.1–114.1)	.873
Weight (kg)	68.85 ± 16.38	65.97 ± 7.85	.605	71.30 ± 9.30	68.27 ± 10.16	.602
Height (cm)	1.71 ± 0.08	1.70 ± 0.06	.649	1.66 ± 0.06	1.69 ± 0.04	.298
BMI (kg/m^2)	21.62 (17.41–38.24)	22.9218.22–29.07	.533	25.65 ± 2.73	23.65 ± 3.098	.263
WC (cm)	80.30 ± 16.69	78.92 ± 9.46	.814	81.44 ± 7.85	83.61 ± 8.49	.656
Hip circumference (cm)	95.51 ± 9.29	95.30 ± 4.96	.948	99.33 ± 7.66	95.50 ± 6.22	.364
WHR	.87 ± .09	.85 ± .053	.552	.91 ± .02	.89 ± .076	.492
Fat (%)	23.50 ± 8.33	20.90 ± 5.45	.397	24.65 ± 4.05	21.10 ± 5.51	.232
Fat Mass (kg)	12.70 (7.30–34.60)	16.10 (7.70–20.80)	.921	17.80 ± 4.94	14.78 ± 5.39	.336
FFM (kg)	51.66 ± 7.87	51.98 ± 5.45	.913	53.50 ± 5.01	53.48 ± 5.87	.996
TBW (kg)	33.34 ± 5.65	34.49 ± 4.86	.616	35.17 ± 3.96	35.87 ± 5.03	.794
Lean Mass (kg)	48.97 ± 7.49	49.22 ± 5.23	.927	50.70 ± 4.75	50.71 ± 5.58	.996
Visceral fat	6.0 (1.0–18.0)	7.0 (2.0–12.0)	.974	10.5 (7.0–14.0)	10.0 (4.0–12.0)	.325
Sistole (mmHg)	110 (100–120)	120 (90–140)	.135	120 (100–126)	110 (100–122)	.363
Diastole (mmHg)	70 (60–80)	80 (60–80)	.033	78 (70–90)	70 (64–82)	.123

Data was displayed in mean(SD) or median(min-max).
*P < 0.05.

that compares the metabolic profiles between FDR and non-FDR of T2DM groups. A similar study was conducted by *Bianco* et al. in Italy on 410 healthy subjects in 2013. They reported that the FDR group had higher BMI and central obesity (hip circumference, WHR) compared to non-FDR and Second-Degree Relatives (SDR) [14]. However, that study did not perform age and gender matching between FDR and non-FDR groups. The study found that the FDR group had a significantly older age compared to non-FDR group. This might affect the results of the study since it is known that there is a strong relationship between advanced age and metabolic disorders. In our study, a matching process was based on gender and age in order to avoid both factors to be the confounding factors in the study.

Our study involved high risk populations who had neither IGT nor hypertension, in order to obtain the initial metabolic disorders in FDR before development of IGT and hypertension. This might be different from the previous studies involving similar population as ours but did not exclude IGT and hypertension. This difference could explain the different results found between our study and the previous studies. The previous studies (Amini et al, Siewert et al, Cederberg et al) found that the differences in most of metabolic profiles (IGT, lipid profile, BMI) were significant between FDR and non-FDR groups, while our study found differences in several variables only, such as lipid profiles.

Type 2 Diabetes Mellitus remains a major health problem with increasing rates in both developed and developing countries, including Indonesia [2,15]. Genetic and environmental factors (lifestyle habits) play an important role in the incidence of T2DM. Obesity is an initial disorder in the course of insulin resistance before the onset of IGT.

The analysis of first data collection involved all FDR and non-FDR groups aimed to get a picture of the proportion of IGT, BMI and lipid profiles between the two groups. *Rane* et al. showed the FDR group had higher BMI [23.37 ± 02.68 kg/m^2 vs. 20.89 ± 03.04 kg/m^2, p < 0.0001], WC [80.56 ± 10.96 cm vs. 78.84 ± 09.19 cm, p < 0.0001] and hip circumference [97.80 ± 08.39 cm vs. 94.26 ± 06.56 cm, p = 0.0030] than the non-FDR group [16] *Cederberg* et al. study in Finland also showed that higher overweight and obesity proportions were found in the FDR group compared to non-FDR [17]. In our study the first data analysis showed that the FDR group had higher BMI, RBG and HbA1c than non-FDR group. The difference in BMI between FDR and non-FDR groups was found to be significant [23.25 (15.80–40.00) kg/m^2 vs. 22.65 (15.62–34.15) kg/m^2, p = 0.034]. In addition, the proportion of overweight and obese in the FDR group was higher than in non-FDR group [68% vs 32%, p = 0.028, 1.977 (1,074–3,638)].

Overweight, obese and centrally obese individuals were at much higher risk of IGT and diabetes than non-obese individuals, which were triggered by physical inactivity, high-fat diet, and diet rich in saturated fatty acids [5,18]. Obesity was associated with chronic low-grade inflammation, characterized by elevated concentration of circulating inflammatory markers. C-reactive Protein (CRP) and Interleukin-6 (IL-6) were inflammatory markers associated with increased risk for T2DM and cardiovascular disease. Therefore, inflammation plays a pivotal role as a link between obesity and several other diseases, like insulin resistance, diabetes mellitus, hypertension and dyslipidemia [19].

Family history of T2DM, especially in FDR, had a high risk of incidence prediabetes and T2DM [5]. A meta-analysis by *Wagner* et al. in Germany of 8106 healthy subjects with a family history of T2DM, reported results of a significant association between family history of T2DM with the risk of the incidence of prediabetes (IFG and/or IGT, OR 1.40; 95% CI 1.27–1.54, p < 0.001). In addition, the study also reported that by adjusting sex, age and BMI values showed a significant relationship between family history of T2DM and prediabetes incidence (OR 1.26; 95% CI 1.14–1.40, p ≤ 0.001) [20]. A study by *Muktabhant* et al. in Thailand reported similar results, as subjects with FDR of T2DM had a higher risk of future T2DM (OR 2.9; 95% CI 1.84–4.57) [21]. Studies in Iran [T2DM (OR: 1.31; 95% CI: 0.96–1.78) and IFG (OR: 1.41; 95% CI: 1.10–1.80)](5)

and in China [30–39 years old, OR: 9.39 (5.77–15.29), p < 0.001] [22] also showed that the FDR group had IGT more often than the non-FDR group. A study in China that involved 46,239 participants with a mean age of 44.9 years, showed that the offsprings of the diabetics are at risk of experiencing a higher glucose tolerance disorder of 3–4 times compared to non-FDR [23]. Previous studies mostly involve adult FDR populations aged above 40 years.

The similiar median value of HbA1c level between FDR and non-FDR groups was observed in our study. However, the minimum and maximum range of values were quite different. This result was very likely to be influenced by the age criteria in our study which only involved participants younger than 40 years old. Based on glucose intolerance status, there was more FDR participants who experienced IGT, when compared to that of non-FDR participants [78.3% vs 21.7%, p = 0.064, OR 2.60 (0.918–7.363)]. In this study, we showed that the IGT in the FDR group started earlier in age than in other studies. Different with ours, the previous studies involved a much larger number of participants with family history of T2DM and also participants with T2DM, therefore showed a significant differences between FDR and non-FDR groups on the results of HbA1c levels [24].

Previous studies by *Purnamasari* et al. [9], *Kumar* et al. [10], *Ogedengbe* et al. [12], and *Siewert* et al. [13] reported that metabolic syndrome was higher in FDR DM subjects compared with non-FDR. Among the components of the metabolic syndrome, central obesity and dyslipidemia are earlier clinical features that appear in high-risk populations. Hypertriglyceridemia and low HDL-C are two lipid profile abnormalities that are common in metabolic syndrome. In this study, we assessed the difference in lipid profiles between FDR and non-FDR groups based on each gender as we did not see any significant difference when we performed the analysis for both genders all together. This might be due to the younger age of the study participants (19–<40 years) when compared to other studies. In addition, our female subjects were in reproductive age <40 years (reproductive age), therefore the presence of estrogen hormone is protective against the onset of metabolic disorders. A study by *Shetty* et al. in India showed that in perimenopausal age there was an increase in TC, TG, LDL-C and decreased HDL-C levels compared to the younger age group of women due to the influence of estrogen hormone on lipid metabolism [25].

A study by *Bianco* et al. in Italy analyzed the metabolic profile of the FDR population by sex and showed that the female FDR group had higher BMI, body surface area, WC and hip circumference than those in non-FDR group [14]. In this study, there were no significant differences in metabolic profiles (BMI, WC, FBG, HbA1c, TC, HDL-C, LDL-C, TG and body composition) between female FDR groups and non-FDR. The subjects range of age in this study was younger than the research participants in *Bianco* et al. study, therefore metabolic differences has not yet to manifest. This can be affected by the presence of estrogen that plays protective role to avoid abdominal fat accumulation, dyslipidemia, obesity and IGT [26].

In male subjects there were differences in metabolic profiles between male FDR and non-FDR groups. In the 30–39 year old group, the male FDR group had higher TC levels [233 ± 51.43 mg/dL vs. 177.83 ± 22.08 mg/dL, p = 0.036] and LDL-C levels [173.83 ± 39.83 mg/dL vs. 125.67 ± 21.50 mg/dL, p = 0.026] than those in the non-FDR group. In the younger age group (19–<30 years) differences in lipid profiles have not been obtained. The male FDR group had more proportion of hypercholesterolemia than the non-FDR group [75% vs 25%, p = 0.031, OR 5.25 (1.09–25.21)]. These findings supported several previous studies regarding lipid profiles in the FDR group, which showed an increase level compared to the non-FDR group. A study by *Lee* et al. in South Korea showed that in non-diabetic participants with family history of T2DM had higher TC levels than those without family history of T2DM [205.3 ± 38.5 mg/dL vs. 202.5 ± 38.4 mg/dL, p = 0.030] [24]. A study by *Gurgel* et al. in Brazil that studied FDR group who suffered from myocardial infarction under the age of 45 compared to non-FDR healthy individuals, a higher LDL-C levels were found in the FDR group [13.8% vs 7.2%, p = 0.045] [27]. This lipid profile and anthropometric changes were associated with insulin resistance that occurred in the FDR group [10]. Disarrangement of lipid metabolism has an impact on insulin resistance. Hypertriglyceridemia and a low HDL-C have been shown to be associated with insulin resistance and IGT [28]. In addition, insulin resistance can also have an impact on lipid profiles, especially for increased TG. Insulin resistance and lipids have a close relationship and abnormality of one value followed by abnormality on another value [29]. The prevalence of insulin resistance was higher in men than women, therefore changes in lipid profile were first seen in the male FDR group compared to the female FDR group [10,30].

The results of this study indicated that the FDR group has a greater risk of metabolic abnormalities when compared to the non-FDR group. The FDR group of men aged over 30 years had a higher risk of dyslipidemia than non-FDR in the same age range. Based on an unpublished report in 2006 in Jakarta, Indonesia, approximately of 30% of males over 30 years old had developed dyslipidemia. This showed that the screening in the FDR population at the age of 30 years had to be more active. In female subjects, the difference in metabolic profiles between FDR and non-FDR groups has not been observed at the age of <40 years, which is very likely to be affected by the protective mechanism of estrogen.

This study has several limitations. First, the small number of samples compared to previous studies might influenced the statistical significance of study results. Family history of diabetes in the control group were obtained from history taking. Although previous studies also recruited the control group by using the same process, the previous studies showed statistically significant results as those studies involved a larger number of subjects.

5. Conclusion

FDR T2DM subjects have a greater BMI compared to non-FDR. Male FDR subjects have 5 times higher risk in developing hypercholesterolemia when compared to non-FDR. This study showed that in male subjects, the difference in metabolic profiles between the FDR and non-FDR groups was found at over 30 years of age, whereas in female subjects the metabolic profile differences were not found under 40 years of age.

Conflicts of interest

None of the authors have any conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.12.019.

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