Atherogenic Lipoprotein Profile in First-Degree Relatives of Individuals with Type 2 Diabetes Mellitus

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ABSTRACT

Background: *First-degree relatives (FDR) of individuals with type 2 diabetes mellitus (T2DM) are at higher risk of developing early metabolic disturbances, particularly insulin resistance and lipid metabolism abnormalities. These issues contribute to a greater predisposition to cardiovascular disease compared to the general population. Despite the significant contribution, there is limited information on the relationship between atherogenic lipoproteins of normotensive and normoglycemic young FDR in Indonesia. Therefore, this study aimed to evaluate the correlation between small dense low-density lipoprotein (sdLDL) levels and HOMA-IR in FDR with T2DM, as well as assess variation in sdLDL levels within FDR and non-FDR groups.* ***Methods:*** *This cross-sectional study analyzed secondary data from the Metabolic Endocrine and Diabetes Division of the Internal Medicine Department, Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo Hospital. The primary study, titled "Early Cardio-Metabolic Disorders in the First-Degree Relative Population of Type 2 Diabetes Mellitus," was expanded to include sdLDL measurements. Bivariate analysis and correlation tests were used to explore the relationship between sdLDL and HOMA-IR.* ***Results:*** *The experiment included 125 subjects consisting of 62 FDR and 63 non-FDR. Based on the results, sdLDL levels were significantly higher in the FDR group compared to the non-FDR group (31.42 (IQR 20.1-41.39) vs 21.05 (IQR 12.18-26.13) mg/dL, $p<0.0001$). However, no significant correlation was observed between sdLDL levels and HOMA-IR in the FDR group ($r=0.059$, $p=0.649$).* ***Conclusion:*** *This study showed a significant difference in sdLDL levels between FDR and non-FDR of T2DM patients. However, no correlation was found between sdLDL and HOMA-IR in the FDR group.*

Keywords: *atherogenic lipoprotein, first-degree relative, type 2 diabetes mellitus, sdLDL*

INTRODUCTION

Diabetes Mellitus (DM) is a global health issue, posing a significant threat to health status. Data from the World Health Organization (WHO) in 2014 showed an increasing prevalence of DM worldwide, with the Southeast and Western Asia regions estimated to have the highest number of patients.[1] In Indonesia, the 2018 Basic Health Research (RISKESDAS) reported a 0.5% increase in DM prevalence among the population aged ≥15 years between 2013 and 2018, showing a similar trend to the global scale.[2]

Type 2 Diabetes Mellitus (T2DM) one of the most common non-communicable diseases, influenced by several risk factors, including genetic predisposition. First-degree relatives (FDR) of T2DM patients are at higher risk of developing T2DM in the future. Although no specific studies have assessed morbidity and mortality in this population, several reports have shown that FDR with T2DM experienced pancreatic beta-cell dysfunction and insulin resistance at a young age, even when glucose tolerance is still normal.[3–7]

Insulin resistance is a key factor in the pathophysiology of metabolic syndrome, which includes central obesity, dyslipidemia, hypertension, and elevated fasting blood glucose levels.[8,9] Several studies have shown a significant prevalence of insulin resistance among FDRs with T2DM.[10,11] This condition increases their risk of developing various metabolic diseases, including metabolic syndrome and cardiovascular diseases in the future, triggered by changes in atherogenic lipid profile, such as elevated small dense low-density lipoprotein (sdLDL). Despite the significant risk, there is limited information regarding atherogenic lipoprotein profiles in FDR with T2DM patients in Indonesia. Therefore, this study aimed to explore the atherogenic lipoprotein profiles in normoglycemic and normotensive FDR with T2DM and evaluate the relationship between insulin resistance and changes in lipid profiles in the high-risk population.

METHODS

Design, Settings, and Respondents

This cross-sectional study analyzed secondary data from the Metabolic Endocrine and Diabetes Division of the Internal Medicine Department, Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo National General Hospital. The primary study is titled "Early Cardio-Metabolic Disorders in the First-Degree Relative Population of Type 2 Diabetes Mellitus." The FDRs group was consisted of biological children of T2DM patients who regularly attended the endocrine clinic. Meanwhile, the non-FDRs group consisted of medical and non-medical staff from the Cipto Mangunkusumo hospital who had no parental history of T2DM. Subjects who signed the informed consent form received blood pressure, random blood glucose, and HbA1c testing using a BioHermes A1c Analyzer to screen for exclusion criteria. Furthermore, subjects who met the inclusion criteria (blood pressure <140/90 mmHg, HbA1c levels between 4–5.6%, and BMI <35 kg/m²) had venous blood drawn after 12 hours of fasting. The blood samples obtained were used for assessment of fasting blood glucose, insulin, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. The remaining serum was centrifuged and stored at -80°C freezer in the Indonesian Medical Education and Research Institute (IMERI) Metabolic Disorder, Cardiovascular, and Aging Cluster (MVA) laboratory. In this study, additional sdLDL testing was performed on the stored serum samples using a sandwich ELISA with human sdLDL (colorimetric) NBP2-82535 ELISA kit by Novus Biologicals.

Statistical Analysis

Data analysis was performed with IBM SPSS Statistics 25.0 and STATA version 17 software. Univariate analysis was conducted to describe the characteristics of the subjects. The difference in mean sdLDL between the FDRs and non-FDRs groups was analyzed using Mann–Whitney U test. Meanwhile, the correlation between sdLDL and HOMA-IR in the FDRs group was analyzed using Spearman's correlation, with a statistical significance level of p<0,05.

Ethical Issues

This study received ethical approval from the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia, with number KET-784/UN2.F1/ETIK/PPM.00.02/2024.

Furthermore, all patient data were kept confidential throughout the study process.

RESULTS

Study Population

A total of 125 subjects were included in the study, consisting of 62 with a parental history of T2DM and 63 without such a history. Age- and sex-matching were conducted for FDR subjects. The median age was 28 years, range: 26-31 years. The distribution of subjects was 65 males (52%) and 60 females (48%). Baseline characteristics of the study population are summarized in **Table 1**.

Mean Difference of SDLDL Levels between FDRs and Non-FDRs Subjects

The analysis showed that the median sdLDL level in FDR subjects was 31.42 mg/dL (range: 20.1–41.39 mg/dL), while the non-FDR group had 21.05 mg/dL (range: 12.18–26.13 mg/dL). Due to the non-normal distribution of data, a non-parametric Mann-Whitney U test was conducted to compare the two groups. The test showed a statistically significant difference in median sdLDL levels between FDR and non-FDR subjects ($p<0.0001$), which remained consistent after stratifying by gender. Among male subjects, median sdLDL levels were 32.69 mg/dL (range:

Table 1. Baseline characteristics of the study population

Variable	All subjects (n=125)	FDRs (n=62)	Non-FDRs (n=63)	P-value
Age (years old), median (IQR)	28 (26 – 31)	28 (26 – 31.25)	27 (26 – 30)	0.355
Gender, n (%)				
Male	65 (52.0)	32 (51.6)	33 (52.4)	1.000
Female	60 (48.0)	30 (48.4)	30 (47.6)	
Family history of T2DM, n (%)				
Father	26 (20.8)	26 (41.9)	0 (0.0)	<0.0001
Mother	32 (25.6)	32 (51.6)	0 (0.0)	
Father and Mother	4 (3.2)	4 (6.5)	0 (0.0)	
None	63 (50.4)	0 (0.0)	63 (100.0)	
BMI (kg/m^2), Mean (SD)	24.20 (4.02)	24.42 (4.22)	23.98 (3.84)	0.543
Male	24.3 (3.93)	24.75 (4.11)	23.86 (3.76)	0.366
Female	24.11 (4.16)	24.08 (4.39)	24.13 (3.99)	0.969
Waist circumference (cm), mean (SD)	74.12 (6.07)	83.35 (10.87)	79.23 (10.09)	0.030
Male	84.12 (11.23)	87.54 (11.08)	80.8 (10.49)	0.014
Female	78.19 (9.12)	78.87 (8.79)	77.51 (9.53)	0.567
TG (mg/dL), median (IQR)	77 (60 – 109)	79 (63.25 – 110.5)	75 (55 – 97)	0.201
Total cholesterol (mg/dL), median (IQR)	191 (160 – 216)	193.5 (164.5 – 205.2)	183 (157 – 220)	0.754
LDL-C (mg/dL), mean (SD)	129.78 (434.23)	130.85 (34.61)	128.73 (34.10)	0.730
HDL-C (mg/dL), median (IQR)	50 (42.5 – 58)	49.5 (41 – 58)	50 (43 – 58)	0.702
Fasting insulin (mIU/L), median (IQR)	7.52 (5.7-9.45)	7.9 (6.2-10)	7.2 (5.3-8.9)	0.120
HOMA-IR, median (RIK)	1.5 (1.10 – 1.85)	1.62 (1.18 – 3.17)	1.45 (1.0 – 1.82)	0.135

Abbreviations: SD=standard deviation; IQR=interquartile range; BMI=body mass index; TG= triglycerides; LDL= Low Density Lipoprotein; HDL= High Density Lipoprotein; HOMA-IR= Homeostatic Model Assesment for Insulin Resistance

13.46–75.21 mg/dL) in the FDR group and 23.01 mg/dL (range: 12.38–41.11 mg/dL) in the non-FDR group (p = 0.005). For female subjects, the median sdLDL levels were 25.17 mg/dL (range: 11.34–65.23 mg/dL) in the FDR group and 20.36 mg/dL (range: 0.89–56.09 mg/dL) in the non-FDR group (p = 0.016). The difference in sdLDL levels FDR and non-FDR subjects is summarized in **Table 2**.

Correlation between sdLDL Levels and HOMA-IR in the FDR Group

There was no significant correlation between sdLDL and HOMA-IR, with an r-value of 0.059 and a p-value of 0.649. The correlation between sdLDL levels and HOMA-IR in the FDR group is presented in **Table 3** and **Figure 1**.

Table 2. Mean Difference of sdLDL Levels between FDR and Non-FDR Subjects

Variable	Group		P-value
	FDRs	Non-FDRs	
SdLDL (mg/dL), median (IQR)	31.42 (20.1 – 41.39)	21.05 (12.18 – 26.13)	<0.0001
Male	32.69 (13.46-75.21)	23.01 (12.38-41.11)	0.005
Female	25.17 (11.34-65.23)	20.36 (0.89-56.09)	0.016

Table 3. Correlation between sdLDL Levels and HOMA-IR in FDRs Group

	HOMA IR	
	r	P
SdLDL	0.059	0.649

Spearman correlation test

DISCUSSION

This study included a specific population comprising FDR subjects without a history of glucose intolerance or hypertension. Previous reports on FDR population often included subjects who already had glucose intolerance,

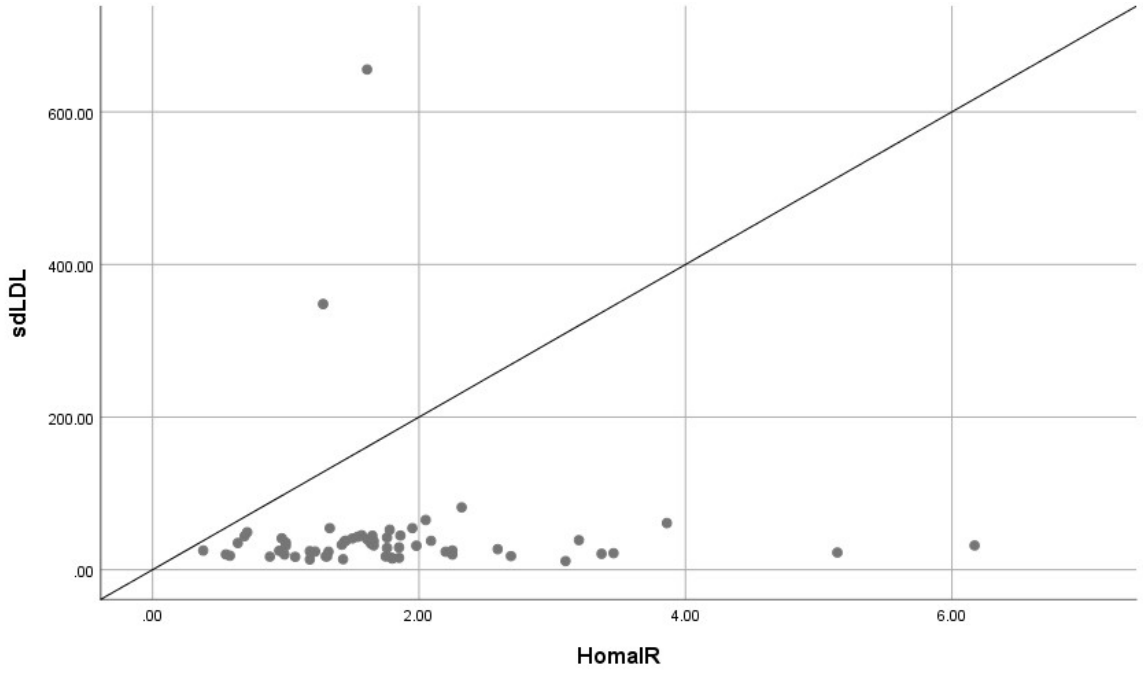

Figure 1. Scatter Plot of the Correlation between sdLDL Levels and HOMA-IR in FDRs Group

such as prediabetes or DM. This distinction is valuable for the early detection of metabolic disturbances in high-risk individuals.

The median age in this study was 28 years (range: 26–31 years), without a significant difference between the FDR and non-FDR groups (28 years [26–31.25] vs. 27 years [26–30], p = 0.355). This study focused on a young FDR population under the age of 40, given that individuals above the age have a higher risk of metabolic disease, regardless of family history. In comparison, Sonuga et al. conducted a study in Nigeria on atherogenic lipoproteins among the FDR population, which included younger subjects aged 18–25, with a mean age of 20 years in the 76 FDRs group and 21 years in the 74 non-FDR group. The variation in results was attributed to differences in inclusion criteria.[12]

Mean Difference of sdLDL Levels between FDRs and Non-FDRs Subjects

There are no previous studies that have directly compared sdLDL levels between FDR and non-FDR groups. However, several reports have examined sdLDL with designs similar to this study. For example, Fan et al. on sdLDL levels in a non-diabetic population in China reported a significant difference in sdLDL values between individuals with and without metabolic syndrome (1.23 [0.95–1.50] vs. 0.94 [0.66–1.20], p<0.001).[13]

SdLDL levels have prognostic value for coronary heart disease (CHD). According to the American Heart Association's "Get With The Guidelines" program, 75% of CHD patients admitted had relatively normal LDL cholesterol levels (<130 mg/dL), and 23% had <70 mg/dL.[14] This suggests that several patients remained at risk for CHD even within normal LDL cholesterol ranges. The atherogenic properties of sdLDL have been confirmed in numerous reports, including the 2009 Malmö Heart Study, the Atherosclerosis Risk in Communities (ARIC), and the Multi-Ethnic Study of Atherosclerosis (MESA) in 2014.[15–17]

The ARIC study found that sdLDL levels above 50 mg/dL were predictive of CHD events. This also included individuals with LDL levels below 100 mg/dL who were previously considered low risk.[18] Similarly, the MESA study reported a significant increase in cardiovascular disease risk with sdLDL levels over 46 mg/dL.[16] A report from Japan also found that LDL levels at 100 mg/dL did not predict CHD risk, but sdLDL levels above 35 mg/dL showed significantly increased risk in patients with stable CHD.[19] In this study, the FDR group showed significantly higher mean sdLDL levels compared with the non-FDR group.

Correlation between sdLDL Levels and HOMA-IR in the FDRs Group

The formation of sdLDL is closely associated with insulin resistance and hypertriglyceridemia, with VLDL1-TG levels serving as a primary predictor of sdLDL particle size.[20,21] Studies investigating the relationship between sdLDL and insulin resistance include Krayenbuehl et al.[22] in Switzerland, who reported a correlation between LDL particle size and insulin resistance, measured by HOMA-IR (r = -0.53, p = 0.001). Similarly, a cohort study by Gerber et al.[23] found a consistent correlation between the proportion of sdLDL particles and insulin resistance (measured by HOMA-IR) both at baseline and after a two-year follow-up (p = 0.04 and p = 0.02, respectively). Based on these results, 70.6% of subjects showed worsened insulin resistance as the proportion of sdLDL increased during the follow-up period.

The differences between this study and the findings of Krayenbuehl et al.[22] and Gerber et al.[23] could be attributed to several factors. Both previous studies included an older population with mean ages of 60 and 63 years. The subjects had been diagnosed with DM (mean duration of 7.2 and 7.3 years), presented with an obese profile obese profile (mean BMI of 30 and 30.5 kg/m²), and showed higher baseline HOMA-IR values (7.9 and 3.36, respectively). In comparison, this study included a younger FDR population with a mean age of 28 years, a lower mean BMI of 24.42 kg/m², and a reduced HOMA-IR of 1.62, indicating minimal or no insulin resistance in the FDR group.

Limitations

This study has several limitations. First, samples were collected only once, which

prevented the ability to assess causal relationships. Second, the DM history of both parents in the non-FDR group was not objectively verified through laboratory testing, which could introduce selection bias. Additionally, factors that could influence insulin sensitivity, such as diet, physical activity, body composition, psychological stress" (avoids repetition of "physical"), psychological stress, and inflammatory parameters, were not assessed.

Generalizability

The results of this study can be applied to the young adult population in Indonesia with FDR of T2DM.

CONCLUSION

In conclusion, **t**here was a significant difference in sdLDL levels between FDR and non-FDR of T2DM patients. However, no correlation was found between sdLDL and HOMA-IR in the FDR group.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest could influence the work reported in this paper.

ABBREVIATIONS

SD: standard deviation; IQR: interquartile range; BMI: body mass index; TG: triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; sdLDL: small, dense Low-Density Lipoprotein.

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