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Gender differences in the distribution of IDL, LDL, and HDL lipoprotein subfractions in MODY compared to type 2 diabetes: Data from the MODY-Ist study

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ABSTRACT

Background: The distribution of intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) subfractions specific to diabetes types and changes under dyslipidemia conditions have been well characterised. Research into the distribution of lipoprotein subfractions in Maturity-Onset Diabetes of the Young (MODY) has hitherto been confined to certain subtypes, with gender-based differences remaining to be elucidated. The objective of this study was to comparatively evaluate the distribution of lipoprotein subfractions according to gender in MODY, T2DM patients, and control groups.

Methods: Lipoprotein subfractions in 119 serum samples of the study groups were analyzed using the Lipoprint-System.

Results: The midbands of IDL (MID-A to C) in female MODY cases, and the HDL-small fraction in male MODY cases, were found to be lower compared to female and male T2DM cases, respectively. In the T2DM group, age was positively correlated with MID-C and MID-B in both genders, while it was negatively correlated with MID-A in female cases. ROC analysis demonstrated that the decrease in the MID-C fraction in female MODY subjects (AUC:0.809, $p = 0.0001$) and the decrease in the HDL-small fraction in male MODY subjects (AUC:0.818, $p = 0.002$) were significantly associated with the likelihood of MODY.

Conclusion: Given that a considerable proportion of MODY patients are frequently misdiagnosed as T2DM, low levels of MID-C and HDL-small fractions, both of which are triglyceride-rich, may have potential as a diagnostic value for female and male MODY patients, respectively.

1. Introduction

Maturity-onset diabetes of the young (MODY) represents the most prevalent form of monogenic diabetes, accounting for 1–2 % of all diabetes cases on a global scale.[1] However, the prevalence of MODY, a frequently misdiagnosed condition due to its clinical features which overlap with those of type 1 (T1DM) and type 2 diabetes (T2DM), is thought to be higher than current estimates.[2] To date, at least 14 different MODY subtypes have been documented, each of which is characterised by a distinct mutation in genes that are predominantly responsible for regulating pancreatic beta cell function.[3] The available evidence has also indicated the potential involvement of other genes in the etiology of MODY (MODYX).[4–7] In addition, it is becoming increasingly evident that other genetic variations associated with T2DM

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may also contribute to the heterogeneity of MODY.[8]

The function of insulin in the regulation of lipid metabolism is a key factor in the development of lipid/lipoprotein disorders in diabetic conditions.[9,10] In the case of insulin resistance, there is a decrease in the inhibitory effect of insulin on the mobilisation of fat from adipose tissue, a decrease in the suppression of lipolysis and an increase in free fatty acids. These pathophysiological changes have been implicated in the development of diabetic dyslipidemia, a condition characterised by hypertriglyceridemia and a decrease in high-density lipoprotein cholesterol (HDL-C) levels.[11] It has been hypothesised that, given the frequent association of diabetic dyslipidemia with T2DM, and the observation that lipid profiles are within normal limits in most MODY subtypes, with the exception of those associated with *HNF4A*-MODY, *HNF1A*-MODY and *HNF1B*-MODY, where low HDL-C and high triglycerides (TG) levels are commonly observed,[12,13] it may be possible to distinguish between MODY and T2DM on the basis of especially HDL-C levels. However, while HDL-C levels are considered useful in differentiating between T1DM, *GCK*-MODY and *HNF1A*-MODY, they are not deemed adequate for distinguishing between T2DM and other MODY subtypes.[14,15]

Recent studies have also documented alterations in the qualitative and kinetic properties of lipoproteins in cases of diabetic dyslipidemia.[10] In T2DM, a decrease in the anti-atherogenic HDL-large fraction (HDL2) and an increase in the atherogenic small, dense fractions of HDL (HDL3) and low-density lipoprotein (sdLDL) are observed, and these changes favor an atherogenic environment, ultimately increasing the risk of cardiovascular disease (CVD).[16–18] The findings have prompted researchers to utilise lipoprotein subfractions in the clinical assessment of CVD and in the early diagnosis of atherosclerotic dyslipidemia in diabetes. However, the majority of research conducted on lipoprotein subfractions has been focused on patients with T1DM and T2DM,[18–20] with research in MODY patients being limited.[15,21] Based on observations of higher levels of HDL phospholipid and cholesterol ester content in patients with *HNF1A*-MODY compared to patients with T2DM, McDonald et al. suggested that HDL-C levels, subfractions, and contents may serve as biomarkers, allowing for the identification of patients with *HNF1A*-MODY.[15] Fendler et al. reported that *GCK-MODY* patients exhibited relatively better metabolic control and a lower risk of cardiovascular complications despite having lower HDL-C levels. They also found that sdLDL concentrations were similar among MODY patients (*GCK-MODY* and *HNF1A-MODY*), T1DM patients, and controls, while antiatherogenic large-buoyant LDL (lbLDL) levels were higher in *GCK-MODY* patients.[21]

The findings of the aforementioned studies suggest that lipoprotein subfractions may exhibit hallmarks for specific types of MODY. However, these studies were conducted exclusively on specific MODY subtypes, and the distribution of lipoprotein subfractions according to gender was not analyzed. In fact, the sex-specific differential effect of insulin on lipid and glucose metabolism is well-established.[22] Lipids and lipoproteins show differences in distribution between men and women from infancy to adulthood.[23] Recent studies have indicated that gender disparities also exist in the subfractionation of LDL and HDL particles among individuals exhibiting atherogenic and non-atherogenic phenotypes.[24]

The objective of this study was to ascertain the concentrations of intermediate-density lipoprotein (IDL), LDL and HDL lipoprotein subfractions and in healthy control, MODY and T2DM groups and to evaluate relationship with clinical and biochemical parameters and the assessment of their potential as biomarkers for the diagnosis of MODY patients based on gender.

2. Materials and methods

2.1. Study population

The study was conducted by comparing three groups, the control group and the MODY and T2DM patient groups. The MODY group was comprised of patients from adult and pediatric endocrinology outpatient clinics of a university who were clinically considered to have MODY based on physical examination and biochemical tests. The MODY cohort was defined based on clinical criteria, including the following: diabetes onset before the age of 40, an autosomal dominant inheritance pattern with diabetes present in at least three generations, including the patient, positive serum C-peptide indicating preserved endogenous insulin secretion, negative pancreatic autoantibodies, absence of ketoacidosis, and clinical features atypical for type 1 or T2DM. All patients meeting these clinical criteria underwent genetic testing for 13 known MODY-associated genes (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, and *KCNJ11*). Given that none of the cases under consideration manifested features consistent with MODY14, analysis of the *APPL1* gene was not performed. Individuals in whom a pathogenic or likely-pathogenic variant was detected were classified as genetically confirmed MODY (MODY*), whereas those with no pathogenic variant identified in any of the 13 genes were classified as MODY-X. Notwithstanding the absence of causative mutations, MODY-X patients manifested a clinical phenotype that was entirely consistent with MODY. This approach ensured that MODY-X classification was based on both comprehensive genetic testing and robust clinical criteria, consistent with published guidelines and clinical prediction models.[4,5] In our previous study (MODY-IST), mutations in different MODY-related genes were identified in 20 of the 32 MODY patients included in this study (**MODY***), but the causative gene could not be identified in 12 patients (**MODY-X**).[6,7] The distribution of MODY* subtypes were as follows: *GCK*-MODY ($n = 1$), *HNF1A*-MODY ($n = 2$), *PDX1/IPF1*-MODY (n = 1), *HNF1B*-MODY (n = 1), *NEUROD1*-MODY ($n = 3$), *KLF11*-MODY (n = 1), *CEL*-MODY (n = 1), *BLK*-MODY ($n = 6$), *ABCC8*-MODY (n = 1), *KCNJ11*-MODY (n = 1), double-heterozygosity of *PDX1*-MODY/*KLF11*-MODY (n = 1), and triple-heterozygosity of *CEL*-MODY/*ABCC8*-MODY/*KCNJ11*-MODY (n = 1) (Suppl. Table 1). The control group consisted of 50 healthy individuals who had no mutations detected in the same project and who did not have diabetes, dyslipidemia, obesity, hyperglycemia or any component of metabolic syndrome in themselves or their first-degree relatives. The study also included 37 cases of T2DM diagnosed according to the current criteria.[25] The subjects had not been diagnosed with CVD and were not receiving lipid-lowering therapy. Furthermore, none of the female subjects in this study were receiving oral contraceptives or hormone replacement therapy.

The study protocol was approved by both the local institutional review board (dated 24/06/2016 and numbered 2016/818)) and the funding body of the university. This study was conducted in accordance with the 2013 version of Declaration of Helsinki. A written informed consent was obtained from all patients and/or their parents.

2.2. Lipoprotein subfraction analysis

The quantitative measurement of lipoprotein subfractions was conducted in serum samples using LipoprintTM Lipoprotein Subfractions Assay Kits, with each kit specifically designed for the separate quantification of LDL and HDL subfractions (Quantimetrix Corp., Redondo Beach, CA). The classification system employed by the manufacturer in the LDL Lipoprint system separates particles into the following categories based on their size: one very low-density lipoprotein (VLDL) particle, three IDL particles (mid-band-C (MID-C, large IDL), -B (MID-B, medium IDL), and -A (MID-A, small IDL)), and seven LDL particles (LDL 1-7). LDL1 and LDL2 are classified as lbLDL, while LDL 3-7 is classified as sdLDL. The Lipoprint HDL system, which separates 10 HDL lipoprotein fractions, classifies HDL 1-3 subfractions as HDL-large, HDL 4-7 subfractions as HDL-medium, and HDL 8-10 subfractions as HDL-small.

2.3. Statistical analysis

All statistical analyses were performed by SPSS software package

(version 20.0 SPSS Inc., IL, USA). The distribution of continuous variables was analyzed using the Kolmogorov-Smirnov (K-S) test to test normality of data. A significant difference in age distribution was observed between the study groups. In order to eliminate the effect of age when comparing continuous variables between groups, covariance analysis (ANCOVA) with Bonferroni post-hoc correction was performed for parameters which demonstrated a normal distribution. In the case of continuous variables were found to be non-normally distributed and/or did not satisfy the ANCOVA criteria (homogeneity of variance, normality of dependent variables and homogeneity of slopes), Quade's non-parametric ANCOVA with Bonferroni post-hoc correction was performed. Continuous variables were presented as mean and standard deviation (SD) for normally distributed and as median and interquartile range (IQR) for not normally distributed data. Nominal categorical data were analyzed using the Chi-square test and were presented as numbers and percentages. Odds ratio (OR) and 95 % confidence intervals (CI) were calculated to determine the relative risks between the study groups. The diagnostic value of lipoprotein subfractions, which exhibited significant differences between the MODY and T2DM groups in the analysis of covariance, was assessed using receiver operating characteristic (ROC) curve analysis. ROC curve analysis was performed in three models including total, female, and male patient groups to determine the cutoff level, the area under the curve (AUC) with 95 % CI, sensitivity, and specificity. Sensitivity and specificity values exceeding 70 %, in the presence of an AUC value greater than 0.70, were regarded as indicative of good diagnostic accuracy. In order to explore potential correlations, the non-parametric Spearman coefficient or the parametric Pearson correlation coefficient were utilized where appropriate. A p value below 0.05 was considered statistically significant.

2.4. Bootstrap-based internal validation of key lipoprotein subfractions

To enhance robustness and provide internal validation given the limited sample size, we calculated bias-corrected and accelerated (BCa) 95 % confidence intervals from 2000 bootstrap resamples of the original data. The bootstrap method was applied to the lipoprotein subfractions (MID-C in women and HDL-small in men) that exhibited significant group differences. Diagnostic performance was quantified by the area under the ROC curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV), likelihood ratios (LR+ and LR−), and overall accuracy derived from ROC analysis, each accompanied by bias-corrected and accelerated (BCa) 95 % confidence intervals to provide internally validated estimates. The bootstrap results were evaluated using two complementary criteria, as recommended in the methodological literature:[26,27] (i) BCa confidence intervals that do not include zero, which indicates a statistically significant group difference; and (ii) consistency in the direction of the bootstrap confidence intervals. This reflects stability in the effect estimate across resamples and provides additional evidence of internal validity.

3. Results

3.1. Clinical characteristics

As expected, the mean age in the MODY group was younger than in the control and T2DM groups ($p < 0.001$). Compared with the T2DM group, the total MODY group had earlier onset of diabetes ($p < 0.001$) and longer duration of diabetes ($p = 0.034$), but other clinical and biochemical findings were similar. Total MODY and T2DM patients exhibited higher systolic blood pressure (SBP), high-sensitivity C-reactive protein (hs-CRP), glycemic parameters, and TG levels than the control group. Clinical and laboratory findings did not differ between MODY* and MODYX groups with the exception of alanine aminotransferase (ALT) levels ($p = 0.014$) (Suppl. Table 2). Due to the limited number of MODY* and MODYX cases, only the total MODY group was used in analyses examining gender effects.

The analyses conducted on subgroups divided by sex revealed that the mean age of both female and male subgroups of the total MODY was younger than that of the T2DM group ($p < 0.001$ and $p = 0.009$, respectively). Female patients with MODY and T2DM exhibited higher mean BMI, SBP, hs-CRP, FBG, HbA1c, TG, TSH and FT4 in comparison to the female control subgroup. A subsequent subgroup analysis of male subjects revealed elevated FBG and HbA1c levels among patients with both MODY and T2DM ($p < 0.001$). Furthermore, the male MODY patients demonstrated increased levels of TG in comparison to the male controls ($p = 0.035$) (Table 1).

3.2. Lipoprotein subfractions

The analysis of LDL and HDL subfractions revealed that the total MODY group exhibited higher LDL3 ($p = 0.041$) and LDL 3-7 ($p = 0.037$) fractions and a lower HDL-intermediate fraction ($p = 0.05$) compared to the control group. Despite the observations indicating similar trends within the MODY* and MODYX subgroups, the results are not statistically significant, probably attributable to the reduced sample size. Patients with T2DM had higher levels of MID-B ($p = 0.011$) and LDL 3-7 ($p = 0.03$), and lower levels of HDL-large ($p = 0.003$) and HDL-intermediate ($p = 0.02$) compared to the control group; however, no significant differences were observed between the T2DM and MODY groups (Suppl. Table 3).

Conversely, a substantial discrepancy in serum levels of lipid subfractions was identified between study subgroups categorised according to gender (Table 2). In female participants, LDL2 levels in the MODY group were higher than those observed in the control group ($p = 0.047$). Female patients with T2DM exhibited higher levels of MID-C ($p = 0.044$), MID-B ($p < 0.001$) and LDL2 fractions ($p = 0.012$), and lower levels of HDL-large and -intermediate fractions ($p < 0.001$ and $p = 0.009$, respectively) compared to female controls. Furthermore, female MODY group had lower levels of MID-C ($p = 0.015$), MID-B ($p = 0.014$) and MID-A ($p = 0.004$) compared to female T2DM. The analysis of male participants indicated that MODY patients exhibited lower levels of HDL-small fraction compared to those with T2DM ($p = 0.038$).

Gender-based comparisons within the study groups revealed that HDL-intermediate ($p = 0.043$), HDL-C ($p = 0.012$), and BMI ($p = 0.048$) levels exhibited higher mean values in women than in men in the MODY group. Furthermore, female patients in the T2DM group demonstrated higher levels of MID-A ($p = 0.005$), HDL-total ($p = 0.002$), and LDL-C ($p = 0.003$) in comparison to male T2DM patients (Tables 1 and 2, p-values not shown for female versus male comparisons).

A subsequent analysis, employing an age-adjusted ANCOVA with 2000 bootstrap resamples, revealed significant sex-specific differences in lipoprotein subfractions between the study groups. In women, MID-C levels were significantly lower in MODY compared with T2DM (mean difference −8.02 mg/dL; BCa 95 %CI: −14.08 to −2.15; p = 0.012), whereas no difference was observed between MODY and controls (mean difference 1.70 mg/dL; BCa 95 %CI: −1.42 to 4.28; $p = 0.276$). Healthy controls exhibited lower MID-C levels compared to T2DM (mean difference −6.32 mg/dL; BCa 95 %CI: −12.38 to −0.90; $p = 0.036$). In the male population, HDL-small levels exhibited a decrease in MODY when compared to both T2DM (mean difference −30.38 mg/dL; BCa 95 %CI: −52.09 to −5.91; $p = 0.016$) and control groups (mean difference −23.55 mg/dL; BCa 95 %CI: −42.86 to −2.04; $p = 0.030$). However, no significant difference was observed between the male subgroups of controls and the T2DM (mean difference −6.83 mg/dL; BCa 95 %CI: −27.46 to 14.51; $p = 0.510$) (Suppl. Table 4). For each significant comparison, the BCa confidence intervals did not include zero, and the direction of the bootstrap estimates remained consistent across 2000 resamples, providing support for the robustness of gender-specific group differences despite the limited sample size.

Table 1
Demographic, biochemical and clinical characteristics of study groups by gender.

Female	Groups			*p* values		
	Control ($n = 28$)	Total MODY ($n = 20$)	T2DM ($n = 23$)	Control vs. total-MODY	Control vs. T2DM	Total-MODY vs. T2DM
Age (year)	36.9 ± 7.4	32.5 ± 16.7	48.7 ± 14.6	0.749	**0.005**	**0.001**
Age at diagnosis (year)	–	23.5 (19.7)	39 (25)	**–**	–	0.074
Duration of DM (year)	–	9.5 (20.7)	11 (13)	**–**	–	0.08
BMI (kg/m^2)	23.03 ± 3.11	26.8 ± 7.2	30.2 ± 7.0	**0.003**	**0.017**	1000
SBP (mmHg)	110.5 ± 2.4	117.8 ± 1.7	132.9 ± 4.9	**0.02**	**0.001**	0.649
DBP (mmHg)	76 (10)	75.6 (5)	80 (20)	1.000	0.141	0.901
hs-CRP (mg/L)	0.7 (1.6)	0.9 (3.6)	2.8 (6.9)	**0.01**	**0.002**	1.000
FBG (mg/dL)	86.6 ± 8.0	169.4 ± 75.6	209.3 ± 140.6	**0.001**	**0.001**	1.000
HbA1c (%)	5.5 ± 0.2	7.3 ± 1.5	8.4 ± 2.6	**0.001**	**0.001**	1.000
C peptide (ng/mL)	–	2.1 (1.0)	2.2 (1.4)	–	**–**	1.000
Triglycerides (mg/dL)	56 (104)	118.5 (75)	137 (76)	**0.003**	**0.001**	1.000
HDL-C (mg/dL)	58.0 ± 16.8	53.8 ± 14.5	45.4 ± 12.4	0.721	0.089	1.000
LDL-C (mg/dL)	106.3 ± 39.9	104.1 ± 28.8	132.9 ± 45.8	1.000	**0.014**	**0.017**
TSH (mIU/L)	1.4 ± 1.0	2.2 ± 1.3	2.6 ± 1.1	**0.048**	**0.005**	0.797
Free T4 (ng/dL)	11.1 ± 6.4	16.4 ± 2.9	16.2 ± 3.3	**0.04**	0.115	1.000
Urea (mg/dL)	23.0 ± 7.0	23.7 ± 12.1	28.6 ± 12.6	1.000	1.000	1.000
Creatinine (mg/dL)	0.71 ± 0.12	0.62 ± 0.24	0.68 ± 0.21	0.273	**0.019**	0.906

Male	Control ($n = 22$)	Total MODY ($n = 12$)	T2DM ($n = 14$)	Control vs. total-MODY	Control vs. T2DM	Total-MODY vs. T2DM
Age (year)	37.6 ± 13.8	25.8 ± 15.9	45.0 ± 18.1	0.119	0.520	**0.009**
Age at diagnosis (year)	–	18.3 ± 12.1	37.2 ± 15.5	–	–	0.183
Duration of DM (year)	–	6.3 (5)	5.5 (11.3)	–	–	0.172
BMI (kg/m^2)	24.7 ± 3.6	21.7 ± 5.8	27.0 ± 4.7	1.000	1.000	0.546
SBP (mmHg)	114 (12.5)	120 (10)	120 (20)	0.145	0.077	1.000
DBP (mmHg)	80 (7)	80 (12.5)	80 (25)	1.000	1.000	1.000
hs-CRP (mg/L)	1.3 (3.7)	0.6 (5.4)	2.9 (12)	0.778	0.176	1.000
FBG (mg/dL)	90 (11.2)	130 (101)	145.5 (130.3)	**0.001**	**0.001**	0.224
HbA1c (%)	5.5 (0.6)	6.2 (4.1)	7.9 (3.4)	**0.001**	**0.001**	0.623
C peptide (ng/mL)	–	2.0 ± 0.82	1.9 ± 1.3	–	–	0.584
Triglycerides (mg/dL)	100.5 (67.7)	121.5 (72.5)	132 (97)	**0.035**	0.587	1.000
HDL-C (mg/dL)	46 (19.8)	32.6 (36)	41 (21.7)	1.000	1.000	1.000
LDL-C (mg/dL)	113.0 ± 37.0	106.3 ± 38.0	109.6 ± 33.6	1.000	1000	0.288
TSH (mIU/L)	2.4 ± 1.6	2.2 ± 1.0	1.8 ± 1.0	1.000	1.000	1.000
Free T4 (ng/dL)	16.4 (2.9)	15.1 (1.8)	14.8 (2.8)	1.000	1.000	1.000
Urea (mg/dL)	28.5 ± 5.9	27.9 ± 8.2	29.9 ± 15.9	0.746	1.000	0.388
Creatinine (mg/dL)	0.86 ± 0.15	0.71 ± 0.28	0.83 ± 0.18	0.373	0.409	1.000

The results are presented as mean ± SD or median (IQR). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; hs-CRP, high-sensitivity-C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; FT_4, free thyroxine.

3.3. ROC analysis

A ROC curve analysis was conducted to ascertain the capacity of the MID-B, MID-C, MID-A and HDL-small fractions to discriminate between MODY and T2DM (Fig. 1). Accordingly, in the total population including both genders, using an MID-C cutoff point of 11.5 mg/dL, MODY cases were detected with 75 % sensitivity and 70.3 % specificity (AUC: 0.734, $p = 0.0002$). In a similar manner, in women, the 11.5 mg/dL MID-C cutoff point exhibited a discriminatory value for MODY with 75 % sensitivity and 78.3 % specificity (AUC: 0.809, $p = 0.0001$). In the male population, the 11.5 mg/dL cutoff point for HDL-small particles was determined to possess diagnostic value for the identification of MODY cases, exhibiting a sensitivity of 83.3 % and a specificity of 75 % (AUC: 0.818, $p = 0.002$).

The bootstrapping ROC analysis demonstrated that both the female MID-C and male HDL-small offered clinically relevant discrimination between MODY and T2DM. In women, a MID-C value >11.5 mg/dL was associated with an approximate threefold increase in the likelihood of T2DM (LR(+): 3.13, BCa 95 %CI: 1.48–8.11), whereas a value ≤11.5 mg/dL markedly reduced the likelihood (LR(−): 0.29, BCa 95 %CI: 0.10–0.63). Within the study cohort, the corresponding predictive values were moderate, with a positive predictive value (PPV) of 78.3 % (BCa 95 %CI: 55.0–92.0 %), a negative predictive value (NPV) of 75.0 % (BCa 95 %CI: 50.0–89.5 %), and an overall accuracy of 76.7 % (BCa 95 %CI: 60.5–86.0). In men, an HDL-small concentration >11.5 mg/dL increased the likelihood of T2DM more than fourfold (LR(+): 4.50, 95 % CI: 1.11–11.14), whereas an HDL-small value ≤11.5 mg/dL was associated with a significant decrease in the likelihood of T2DM (LR(−): 0.30, 95 %CI 0.00–0.86). The predictive values in men were of similar magnitude, with a PPV of 75.0 % (BCa 95 %CI: 25.0–100.0 %), a NPV of 83.3 % (BCa 95 %CI: 50.0–100.0 %), and an overall accuracy of 80.0 % (Suppl. Table 5). Despite the relatively wide BCa confidence intervals—particularly in the male subgroup due to the limited sample size—these estimates consistently supported the discriminatory value of MID-C and HDL-small sex-specific lipoprotein subfractions.

3.4. Correlation analysis

Pearson or Spearman correlation analysis demonstrated a positive correlation between the MID-C and MID-B fractions, and between both fractions and VLDL in all study groups. The MID-C fraction has demonstrated a positive correlation with LDL2 in female, LDL1 in male, and LDL 1 + 2 and LDL-C in both genders. In line with these results, MID-C was positively correlated with LDL-C in both genders in the MODY group, and negatively correlated with HDL-large in female cases. In the T2DM cohort, MID-C fraction showed a strong positive correlation with age in male subjects and a weak one in female subjects. MID-C was also found to be positively associated with LDL-C and duration of diabetes in male subjects and with HDL-small in female subjects of T2DM group. The MID-B fraction exhibited a positive correlation with LDL1 and LDL-

Table 2
Comparison of lipoprotein subfractions in study groups according to gender.

Female	Groups			p values		
	Control (n = 28)	Total MODY (n = 20)	T2DM (n = 23)	Control vs. total-MODY	Control vs. T2DM	Total-MODY vs. T2DM
VLDL	16.8 ± 4.1	16.4 ± 5.7	22.9 ± 9.6	0.861	0.223	0.401
MID-C	12.5 ± 4.4	10.2 ± 4.2	20.6 ± 12.8	1.000	**0.044**	**0.015**
MID-B	4 (3.5)	6 (2.5)	10.5 (6.8)	1.000	**<0.001**	**0.014**
MID-A	11.8 ± 5.0	8.9 ± 2.9	12.2 ± 5.6	0.058	0.694	**0.004**
LDL1	19.4 ± 7.8	17.9 ± 7.9	23.0 ± 12.0	1.000	0.795	0.338
LDL2	5.6 ± 3.0	9.7 ± 5.8	11.9 ± 9.5	**0.047**	**0.012**	1.000
LDL3	2 (1)	3 (5.8)	2 (8.2)	0.295	0.319	1.000
LDL 1+2	25.3 ± 9.7	27.5 ± 11.3	34.9 ± 19.4	1.000	0.150	0.786
LDL 3-7	2 (1)	3.5 (8.5)	2 (1.3–13.8)	0.244	0.256	1.000
Total-HDL	30.8 ± 7.4	28.1 ± 7.2	33.9 ± 7.3	0.698	0.666	0.091
HDL-large	17 (11)	13.5 (15)	11.5 (8.5)	0.078	**<0.001**	0.131
HDL-intermediate	25.9 ± 4.9	22.4 ± 6.0	20.4 ± 6.5	0.087	**0.009**	0.910
HDL-small	11.5 ± 4.1	11.7 ± 3.4	11.6 ± 5.1	1.000	1.000	1.000

Male	Control (*n* = 32)	Total MODY (n = 12)	T2DM (n = 14)			
VLDL	19.2 ± 6.3	19.9 ± 9.8	16.6 ± 5.4	0.861	1.000	0.401
MID-C	14.7 ± 5.4	11.0 ± 5.0	13.9 ± 8.2	1.000	0.827	1.000
MID-B	7.8 ± 3.9	6.9 ± 2.0	9.6 ± 8.6	1.000	1.000	1.000
MID-A	10.1 ± 4.7	11.0 ± 7.4	7.3 ± 3.3	1.000	0.491	0.397
LDL1	20.8 ± 9.9	22.5 ± 7.5	15.6 ± 8.4	1.000	0.450	0.518
LDL2	8.9 ± 5.5	10.6 ± 6.1	10.3 ± 7.7	1.000	1.000	1.000
LDL3	2.1 ± 1.4	3.2 ± 1.2	3.3 ± 1.9	0.748	0.456	1.000
LDL 1 + 2	28.7 ± 15.1	31.9 ± 11.1	25.9 ± 15.5	1.000	1.000	1.000
LDL 3–7	2.6 ± 2.2	5.6 ± 4.9	7.0 ± 5.8	0.455	0.434	1.000
Total-HDL	28.5 ± 5.6	27.8 ± 7.4	24.0 ± 4.2	1.000	0.201	0.875
HDL-large	12.7 ± 6.1	13.0 ± 9.5	9.4 ± 5.0	1.000	0.501	1.000
HDL-intermediate	19.9 ± 5.0	17.2 ± 6.8	17.4 ± 5.5	0.075	0.530	1.000
HDL-small	12.7 ± 4.0	9.2 ± 4.5	13.5 ± 3.2	0.102	1.000	**0.038**

The results are presented as mean ± SD or median (IQR). All data are expressed as mg/dL.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MID-A, small intermediate-density lipoprotein (IDL) particles; MID-B, medium-sized IDL particles; MID-C, large IDL particles; VLDL-C, very low-density lipoprotein cholesterol.

C in both male and female subjects with MODY. In the T2DM group, MID-B demonstrated a positive correlation with age, LDL 3-7, and TG in male patients, and with LDL-C in female patients. In female MODY cases, MID-A showed a positive correlation with LDL1, LDL 1+2, and LDL-C, while it showed a negative correlation with LDL 3-7. In the T2DM group, MID-A demonstrated a positive correlation with LDL1, LDL 1+2, and LDL-C in both female and male patients. Furthermore, an inverse relationship between MID-A and age was identified in female patients, and between MID-A and BMI in male patients in the T2DM group. The HDL-small fraction exhibited a positive correlation with HDL-C in female subjects and with both HDL-C and HDL-large in male subjects within the MODY group. This fraction demonstrated a positive correlation with MID-C, MID-A, LDL1, LDL2, and LDL-C in female cases of T2DM, and with HDL-C in male T2DM cases (Suppl. Table 6).

4. Discussion

Impaired lipid metabolism in patients with T2DM contributes to the development of diabetic dyslipidemia, which is characterised by elevated TG and reduced HDL concentrations. The lipoprotein subfractionation analysis revealed that the dyslipidemic profile was associated with a decrease in anti-atherogenic large and intermediate HDL fractions, and an increase in atherogenic HDL-small and sdLDL fractions. Furthermore, an abnormal distribution of VLDL, LDL, and HDL lipoprotein subfractions has been demonstrated not only in overt T2DM cases but also in prediabetic patients, where elevated HDL-small levels and VLDL size were identified independently of insulin resistance.[28] Although dyslipidemia has been documented in *HNF4A*-MODY, *HNF1A*-MODY, and *HNF1B*-MODY subtypes, the majority of MODY subtypes generally exhibit lipid levels within the normal range.[13,15] Consequently, the assessment of LDL and HDL lipoprotein fractions might provide crucial parameters for the clinical diagnosis of MODY, as their profiles could be distinct from those observed in T2DM patients. The prominent findings of the current research demonstrate that IDL fractions (MID-C, MID-B and MID-A) exhibited reduced levels in female MODY patients, and the HDL-small fraction in male MODY patients, as compared to their respective values in female and male T2DM patients, respectively. ROC analyses and BCa bootstrap estimates support the practical utility of low levels of MID-C in women and HDL-small in men as indicators to help prioritize genetic testing in patients with suspected MODY.

In the present study, a comparison with gender-matched controls revealed that female patients with both MODY and T2DM exhibited elevated BMI, glycemic parameters, blood pressure, TG and hs-CRP levels. In contrast, male MODY and T2DM patients exhibited no substantial disparities, with the exception of elevated glycemic parameters. The present findings are consistent with those of recent studies reporting an increased prevalence of obesity and dyslipidemia in MODY, although these observations pertain specifically to female patients.[13,29]

One of the key metabolic abnormalities associated with diabetes is an alteration in the production and clearance of plasma lipoproteins.[10] In patients with T2DM, there is an increased synthesis of VLDL and a decreased uptake of VLDL and IDL by the liver, resulting in elevated plasma concentrations of these lipoproteins. It is well established that insulin resistance, a pathological component of T2DM, also leads to an augmentation in VLDL via a decreasing lipoprotein lipase (LPL) activity.[30] Concurrently, the hydrolysis of large VLDL by LPL into IDL and their subsequent remodelling by HL leads to the conversion of triglyceride-rich LDL into sdLDL particles.[31] Previous reports have suggested that increased sdLDL particle levels in T2DM patients may represent a possible mechanism underlying the increased incidence of cardiovascular complications.[31,32] Evidence demonstrating that sdLDL fractions increase concurrently with IDL in patients with diabetes, even in the absence of hyperlipidaemia, is of particular importance.[31,33]

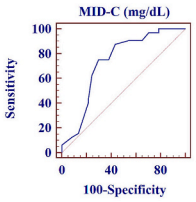
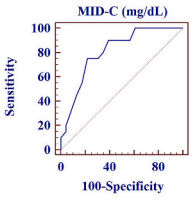
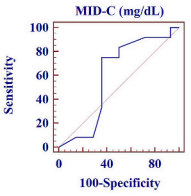
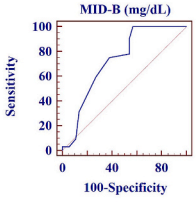
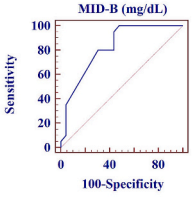
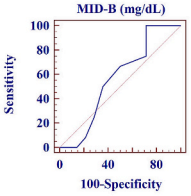
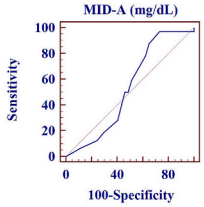
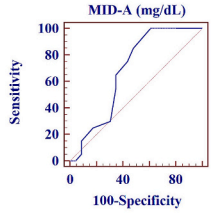
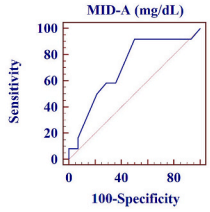
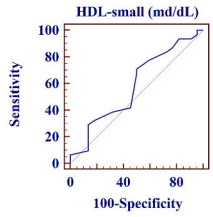
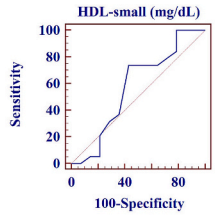
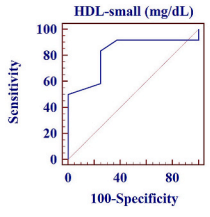
	Total group	Female subgroup	Male subgroup
MID-C	 AUC (95% CI): 0.734 (0.614-0.833) Sensitivity: 75% Specificity: 70.3% Cutoff: 11.5 mg/dL **p value: 0.0002**	 AUC (95% CI): 0.809 (0.660-0.912) Sensitivity: 75% Specificity: 78.3% Cutoff: 11.5 mg/dL **p value: 0.0001**	 AUC (95% CI): 0.595 (0.386-0.782) Sensitivity: 75% Specificity: 64.3% Cutoff: 9.5 mg/dL p value: 0.433
MID-B	 AUC (95% CI): 0.727 (0.606-0.827) Sensitivity: 100% Specificity: 43.2% Cutoff: 7.5 mg/dL **p value: 0.0002**	 AUC (95% CI): 0.822 (0.675-0.921) Sensitivity: 100% Specificity: 52.2% Cutoff: 7.5 mg/dL **p value: 0.0001**	 AUC (95% CI): 0.562 (0.356-0.754) Sensitivity: 100% Specificity: 28.6% Cutoff: 6.5 mg/dL p value: 0.596
MID-A	 AUC (95% CI): 0.533 (0.408-0.654) Sensitivity: 96.9% Specificity: 27% Cutoff: 9.5 mg/dL p value: 0.650	 AUC (95% CI): 0.680 (0.521-0.814) Sensitivity: 100% Specificity: 39.1% Cutoff: 9.0 mg/dL **p value: 0.033**	 AUC (95% CI): 0.702 (0.492-0.864) Sensitivity: 91.7% Specificity: 50% Cutoff: 8.5 mg/dL p value: 0.059
HDL-small	 AUC (95% CI): 0.584 (0.441-0.718) Sensitivity: 71% Specificity: 50% Cutoff: 10.5 mg/dL p value: 0.305	 AUC (95% CI): 0.573 (0.390-0.743) Sensitivity: 73.7% Specificity: 57.1% Cutoff: 10.5 mg/dL p value: 0.508	 AUC (95% CI): 0.818 (0.583-0.952) Sensitivity: 83.3% Specificity: 75% Cutoff: 11.5 mg/dL **p value: 0.002**

Fig. 1. ROC analysis of selected lipid subfractions for total MODY versus T2DM.
ROC, receiver operator characteristic; AUC, area under the ROC curve; CI, confidence intervals.

Furthermore, the exchange of neutral lipids (cholesterol esters/TG) between HDL and VLDL/LDL via the cholesterol ester transfer protein (CETP) has been demonstrated to increase the triglyceride-rich HDL-small fraction in T2DM.[34] The current findings from studies of nuclear magnetic resonance spectroscopy that have also provided evidence that the prevalence of HDL-small particles is higher compared to HDL-large particles in both patients with T2DM[35,36] and prediabetic individuals, with a more pronounced association with the degree of insulin resistance.[25,37]

A recent study reported an association between the triglyceride content in sdLDL and VLDL fractions, as well as the phospholipids in the VLDL-1 (large VLDL) fraction, and T2DM. In contrast, free cholesterol in the HDL-large fraction exhibited an inverse relationship.[38] In the present study, despite the observation of elevated TG levels in the total MODY

and T2DM groups in comparison to the control group, no discrepancy was identified in VLDL levels. As the Lipoprint test does not involve the VLDL fractionation, the direct measurement of triglyceride-rich VLDL-large concentrations was not a possibilitity in the present study. However, increased levels of both TG and sdLDL in the MODY and T2DM groups are indicative of an increase in VLDL-large particles.[39] We also observed positive correlations between triglyceride-rich MID-C and MID-B fractions and VLDL in all study groups, as well as between MID-B and LDL 3-7 in male T2DM subjects. These results provide supplementary evidence for this relationship. Furthermore, the increases in sdLDL levels observed in patients diagnosed with T2DM and MODY occurred concomitantly with decreases in HDL-large (in both T2DM and MODY) and HDL-intermediate (in T2DM) fractions, as well as with increases in TG levels (in both groups) and the MID-B fraction (in T2DM). The reduced HDL-large and HDL-intermediate levels observed in women with T2DM compared to healthy women are consistent with the findings of previous reports.[16,36] In this study, for the first time, a decline in HDL-large and HDL-intermediate levels was observed in the total MODY group (similar to T2DM), although the difference was only significant for HDL-intermediate. This trend was also evident in female MODY patients, although it did not attain statistical significance. Moreover, analyses conducted stratified by gender also revealed elevated LDL2 levels in female participants diagnosed with MODY and T2DM, as well as increased MID-B levels in women with T2DM compared to healthy women. Our findings that MID-C, MID-B and MID-A levels were lower in female MODY cases compared to female T2DM cases, and that HDL-small fraction was lower in male MODY patients compared to T2DM men, are particularly noteworthy. A gender-stratified ROC analysis revealed that a decline in the MID-C fraction in women (AUC = 0.809, $p < 0.0001$) and a decrease in the small HDL fraction in men (AUC = 0.818, $p = 0.002$) could differentiate MODY from T2DM. The bootstrap-based BCa 95 % confidence intervals confirmed the diagnostic performance of these markers at the corresponding optimal cutoff values (MID-C 11.5 mg/dL in women; HDL-small 11.5 mg/dL in men). When evaluated in conjunction with the observation of increased sdLDL levels and decreased HDL-large levels in MODY and T2DM, these results indicate that although MODY and T2DM share overlapping lipid metabolism abnormalities, the specific patterns in MODY are not identical to those in T2DM.

Men and women exhibit differences in their basic lipid and lipoprotein profiles throughout adulthood. Women generally exhibit higher HDL-C and lower triglyceride levels than men before menopause, while men tend to have higher VLDL-C and LDL-C concentrations and lower HDL-C levels throughout most of their lives.[23] These gender-specific patterns are largely determined by hormonal influences, particularly the protective effects of estrogen in premenopausal women. With advancing age and the transition to menopause, women undergo a well-documented shift toward a more atherogenic lipid profile. The decline in estrogen levels during the postmenopausal period has been demonstrated to induce an increase in plasma LPL and HL activity, both of which are regulated by estrogen.[40] Triglyceride and VLDL concentrations rise, LDL cholesterol increases, and the lipoprotein profile shifts toward a more atherogenic structure as circulating estrogen decreases; LDL particles become smaller and denser, HDL shifts from larger HDL_2 subfractions to smaller HDL_3 subfractions, and VLDL remnants (IDL) become more abundant.[24]

In the present cohort, female patients with T2DM were on average older and more frequently postmenopausal than female patients with MODY. Given that VLDL is the sole precursor of IDL, the increase in IDL's MID-C, MID-B (both triglyceride-rich) and MID-A (cholesterol-rich) fractions in female T2DM patients compared to female MODY patients may be attributed to the increase in VLDL. A recent study demonstrated that levels of LDL, IDL, and VLDL increase with age in women with diabetes.[41] This report is also confirmed by studies reporting increased LDL, VLDL and IDL levels in postmenopausal women.[42] Moreover, it has been documented that while high VLDL levels remain constant irrespective of the stage of diabetic nephropathy, IDL levels exhibit a gradual increase concomitant with disease progression.[43] In our study, the lower IDL fractions observed in female MODY patients, considering their younger mean age and milder diabetes, are consistent with the aforementioned reports. These observations underscore the necessity of incorporating age and menopausal status into the interpretation of sex-specific lipoprotein subfraction patterns in monogenic diabetes.

Elevated levels of sdLDL and HDL-small have been demonstrated to be associated with increased HL activity, which hydrolyses TG and phospholipids in LDL-C and HDL-C.[44] It has been demonstrated that HL exhibits a higher affinity for HDL-large than for HDL-small. In particular, in cases of diabetes with elevated TG levels, the high-affinity hydrolysis of HDL-large by HL has been associated with a decrease in HDL-large levels and an increase in HDL-small levels.[45] Furthermore, increased HL activity has been documented in males, augmented intra-abdominal fat, and advanced age.[44] Taking these reports into consideration, the difference in HDL-small levels observed between the male patients of MODY and T2DM groups, both of which had elevated TG levels, may be attributed to the older mean age of the males in the T2DM group and, consequently, higher HL activity.

We observed a positive correlation between age and MID-C and MID-B in patients with T2DM, and a negative correlation between age and MID-A in female subjects in the T2DM and control groups, indicating that MID-C and MID-B fractions increase with age, while MID-A fraction decreases with age. A noteworthy observation is the correlation between higher BMI and higher MID-C fractions, particularly in female MODY cases, along with an analogous increase in HDL-small, evident in male MODY cases. Due to the limited sample size, these relationships could not be further analyzed in the present study and require investigation in larger cohorts in the future. These findings are consistent with recent publications reporting that TG concentrations in VLDL, IDL, LDL, and HDL subfractions increase with increasing age and BMI.[46] Consequently, within the scope of this study, the lower MID-C and MID-B levels observed in the MODY group compared to the T2DM cohort, particularly in female patients, may be attributed to the relatively younger age of the MODY cohort. Despite the decline observed in the MID-A fraction with age, it still exhibited elevated levels in the female T2DM group compared to the female MODY group. Furthermore, the MID-C and MID-A levels were found to have a positive correlation with diabetes duration in male cases of T2DM. The present observations are consistent with the findings of Shoi et al., who reported that total IDL levels increase with T2DM progression.[43]

Given the absence of an independent validation cohort, the reliability of our findings was strengthened by bootstrap approach estimates of age-adjusted ANCOVA models. These models produced BCa confidence intervals that were consistent across resamples and did not include zero, suggesting that the observed sex-specific differences (lower MID-C in female MODY and lower HDL-small in male MODY) are unlikely to be due to random sampling variation. While these results provide internal validity and support the robustness of our findings, the lack of an independent external validity cohort remains a significant limitation. To validate these exploratory observations and confirm their potential diagnostic utility in distinguishing MODY from T2DM, larger, multicenter studies are needed. The second limitation of this study is the small sample size. However, given that MODY is a rare type of diabetes and the present study is the first to examine lipoprotein subfractions, our findings can be considered pioneering. Thirdly, due to the limited number of MODY* and MODY-X cases, lipoprotein subfractions could not be evaluated separately in these groups; instead, they were analyzed in the total MODY group (MODY* and MODY-X). Finally, the activities of LPL and HL enzymes, which influence the levels of lipoprotein subfractions, could not be measured.

In conclusion, the current findings indicate that triglyceride-rich MID-C and HDL-small fractions are lower respectively, in female and male MODY patients than in corresponding gender groups of T2DM. It is important to note that a considerable number of MODY patients are

frequently misdiagnosed as T2DM. In light of this, a comprehensive assessment of serum lipoprotein fractionation has the potential to serve as a valuable diagnostic tool, assisting in the identification of MODY prior to genetic diagnosis. This approach can play a crucial role in ensuring that patients receive the correct diagnosis by referring them for genetic testing. However, first and foremost, further validation is needed through additional studies involving larger, particularly age-matched MODY and T2DM cohorts to support these observations.

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CRediT authorship contribution statement

Hulya Yilmaz Aydogan: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Deniz Kanca Demirci:** Methodology, Data curation. **Nurdan Gul:** Investigation, Data curation. **Fatih Yanar:** Writing – original draft, Software. **Sukran Poyrazoglu:** Resources, Investigation, Data curation. **Seda Gulec Yilmaz:** Methodology, Investigation. **Mete Bora Tuzuner:** Validation, Investigation. **Turgay Isbir:** Resources, Methodology, Investigation. **Oguz Ozturk:** Software, Investigation. **Ilhan Satman:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Peixoto-Barbosa R, Reis AF, Giuffrida F. Update on clinical screening of maturity-onset diabetes of the young (MODY). *Diabetol Metab Syndr*. 2020;12:50. https://doi.org/10.1186/s13098-020-00557-9.
2. Shields B, Hicks S, Shepherd M, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*. 2010;53:2504–2508. https://doi.org/10.1007/s00125-010-1799-4.
3. Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. *Curr Diab Rep*. 2018;18:58. https://doi.org/10.1007/s11892-018-1024-2.
4. Kleinberger JW, Pollin TI. Undiagnosed MODY: time for action. *Curr Diab Rep*. 2015;15:110. https://doi.org/10.1007/s11892-015-0681-7.
5. Zhou Q, Samadli S, Zhang H, Zheng X, Zheng B, Zhang A, et al. Molecular and clinical profiles of pediatric monogenic diabetes subtypes: comprehensive genetic analysis of 138 patients. *J Clin Endocrinol Metab*. 2024, dgae779. https://doi.org/10.1210/clinem/dgae779.
6. Demirci DK, Darendeliler F, Poyrazoglu S, Al ADK, Gul N, Tutuncu Y, et al. Monogenic childhood diabetes: dissecting clinical heterogeneity by next-generation sequencing in maturity-onset diabetes of the young. *OMICS*. 2021;25:431–449. https://doi.org/10.1089/omi.2021.0081.
7. Aydogan HY, Gul N, Demirci DK, Mutlu U, Gulfidan G, Arga KY, et al. Precision diagnosis of young maturity-onset diabetes of the with next-generation sequencing: findings from the MODY-IST study in adult patients. *OMICS*. 2022;26:218–235. https://doi.org/10.1089/omi.2022.0006.
8. Yilmaz-Aydogan H, Kanca-Demirci D, Gul N, Aydogan C, Poyrazoglu S, Tutuncu Y, et al. Target gene variations of PPAR isoforms may contribute to MODY heterogeneity: a preliminary comparative study with type 2 diabetes. *Diabetes Res Clin Pract*. 2024;218, 111932. https://doi.org/10.1016/j.diabres.2024.111932.
9. Rivellese AA, Vaccaro O, Patti L. The pathophysiology of lipid metabolism and diabetes. *Int J Clin Pract*. 2004;58:32–35. https://doi.org/10.1111/j.1368-504X.2004.00332.x.
10. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. *Diabetes Ther*. 2016;7:203–219. https://doi.org/10.1007/s13300-016-0167-x.
11. Carmena R. Type 2 diabetes, dyslipidemia, and vascular risk: rationale and evidence for correcting the lipid imbalance. *Am Heart J*. 2005;150:859–870. https://doi.org/10.1016/j.ahj.2005.04.027.
12. Urakami T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. *Diabetes Metab Syndr Obes*. 2019;12:1047–1056. https://doi.org/10.2147/DMSO.S179793.
13. Satman I. Clinical manifestations and biomarkers of the maturity-onset diabetes of the young. *Endocrine Res Pract (Formerly TJEM)*. 2023;27:98–112. https://doi.org/10.5152/erp.2023.253.
14. Fendler W, Borowiec M, Antosik K, Szadkowska A, Deja G, Jarosz-Chobot P, et al. HDL cholesterol as a diagnostic tool for clinical differentiation of GCK-MODY from HNF1A-MODY and type 1 diabetes in children and young adults. *Clin Endocrinol (Oxf)*. 2011;75:321–327. https://doi.org/10.1111/j.1365-2265.2011.04052.x.
15. McDonald TJ, McEneny J, Pearson ER, Thanabalasingham G, Szopa M, Shields BM, et al. Lipoprotein composition in HNF1A-MODY: differentiating between HNF1A-MODY and type 2 diabetes. *Clin Chim Acta*. 2012;413:927–932. https://doi.org/10.1016/j.cca.2012.02.005.
16. Mora S, Otvos JD, Rosenson RS, Pradhan A, Buring JE, Ridker PM. Lipoprotein particle size and concentration by nuclear magnetic resonance and incident type 2 diabetes in women. *Diabetes*. 2010;59:1153–1160. https://doi.org/10.2337/db09-1114.
17. Dullaart RP, Otvos JD, James RW. Serum paraoxonase-1 activity is more closely related to HDL particle concentration and large HDL particles than to HDL cholesterol in type 2 diabetic and non-diabetic subjects. *Clin Biochem*. 2014;47:1022–1027. https://doi.org/10.1016/j.clinbiochem.2014.04.013.
18. Kamijo Y, Ishii H, Yamamoto T, Kobayashi K, Asano H, Miake S, et al. Potential impact on lipoprotein subfractions in type 2 diabetes. *Clin Med Insights Endocrinol Diabetes*. 2019;12, 1179551419866811. https://doi.org/10.1177/1179551419866811.
19. Jin JL, Zhang HW, Cao YX, Liu HH, Hua Q, Li YF, et al. Association of small dense low-density lipoprotein with cardiovascular outcome in patients with coronary artery disease and diabetes: a prospective, observational cohort study. *Cardiovasc Diabetol*. 2020;19:45. https://doi.org/10.1186/s12933-020-01015-6.
20. Cree-Green M, Maahs DM, Ferland A, Hokanson JE, Wang H, Pyle L, et al. Lipoprotein subfraction cholesterol distribution is more atherogenic in insulin resistant adolescents with type 1 diabetes. *Pediatr Diabetes*. 2016;17:257–265. https://doi.org/10.1111/pedi.12277.
21. Fendler W, Rizzo M, Borowiec M, Malachowska B, Antosik K, Szadkowska A, et al. Less but better: cardioprotective lipid profile of patients with GCK-MODY despite lower HDL cholesterol level. *Acta Diabetol*. 2014;51:625–632. https://doi.org/10.1007/s00592-014-0567-1.
22. Varlamov O, Bethea CL, Roberts Jr CT. Sex-specific differences in lipid and glucose metabolism. *Front Endocrinol (Lausanne)*. 2015;5, 241. https://doi.org/10.3389/fendo.2014.00241.
23. Holven KB, Roeters van Lennep J. Sex differences in lipids: a life course approach. *Atherosclerosis*. 2023;384, 117270. https://doi.org/10.1016/j.atherosclerosis.2023.
24. Zitnanova I, Oravec S, Janubova M, Konarikova K, Dvorakova M, Laubertova L, et al. Gender differences in LDL and HDL subfractions in atherogenic and nonatherogenic phenotypes. *Clin Biochem*. 2020;79:9–13. https://doi.org/10.1016/j.clinbiochem.2020.02.002.
25. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2025. *Diabetes Care*. 2025;48:S27–S49. https://doi.org/10.2337/dc25-S002.
26. Zimmermann G, Pauly M, Bathke AC. Small-sample performance and underlying assumptions of a bootstrap-based inference method for a general analysis of covariance model with possibly heteroskedastic and nonnormal errors. *Stat Methods Med Res*. 2019;28:3808–3821. https://doi.org/10.1177/0962280218817796.
27. Becher M, Hothorn LA, Konietschke F. Analysis of covariance in general factorial designs through multiple contrast tests under variance heteroscedasticity. *Stat Med*. 2025;44, e70018. https://doi.org/10.1002/sim.70018.
28. Festa A, Williams K, Hanley AJ, Otvos JD, Goff DC, Wagenknecht LE, et al. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2005;111:3465–3472. https://doi.org/10.1161/CIRCULATIONAHA.104.512079.
29. Calapkulu M, Ozturk Unsal I, Erkam Sencar M, Sakiz D, Ozbek M, Cakal E. Prevalence of obesity and dyslipidemia in maturity onset diabetes of the young patients. *Endocrinol Res Pract*. 2025;29:9–14. https://doi.org/10.5152/erp.2025.24545.
30. Pont F, Duvillard L, Florentin E, Gambert P, Vergès B. Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity. *Arterioscler Thromb Vasc Biol*. 2002;22:1726–1732. https://doi.org/10.1161/01.atv.0000032134.92180.41.
31. Luciani L, Pedrelli M, Parini P. Modification of lipoprotein metabolism and function driving atherogenesis in diabetes. *Atherosclerosis*. 2024;394, 117545. https://doi.org/10.1016/j.atherosclerosis.2024.117545.
32. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2020;41:2313–2330. https://doi.org/10.1093/eurheartj/ehz962.
33. Yoshino G, Hirano T, Kazumi T. Atherogenic lipoproteins and diabetes mellitus. *J Diabetes Complications*. 2002;16:29–34. https://doi.org/10.1016/s1056-8727(01)00199-4.

34. Dullaart RPF, Pagano S, Perton FG, Vuilleumier N. Antibodies against the C-terminus of ApoA-1 are inversely associated with cholesterol efflux capacity and HDL metabolism in subjects with and without type 2 diabetes mellitus. *Int J Mol Sci*. 2019;20:732. https://doi.org/10.3390/ijms20030732.
35. Cardner M, Yalcinkaya M, Goetze S, Luca E, Balaz M, Hunjadi M, et al. Structure-function relationships of HDL in diabetes and coronary heart disease. *JCI Insight*. 2020;5, e131491. https://doi.org/10.1172/jci.insight.131491.
36. Sokooti S, Flores-Guerrero JL, Kieneker LM, Heerspink HJL, Connelly MA, Bakker SJL, et al. HDL particle subspecies and their association with incident type 2 diabetes: the PREVEND study. *J Clin Endocrinol Metab*. 2021;106:1761–1772. https://doi.org/10.1210/clinem/dgab075.
37. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52: 453–462. https://doi.org/10.2337/diabetes.52.2.453.
38. Gadgil MD, Herrington DM, Singh SK, Kandula NR, Kanaya AM. Association of lipoprotein subfractions with incidence of type 2 diabetes among five U.S. race and ethnic groups: the Mediators of Atherosclerosis in South Asians Living in America (MASALA) and Multi-Ethnic study of Atherosclerosis (MESA). *Diabetes Res Clin Pract*. 2023;204, 110926. https://doi.org/10.1016/j.diabres.2023.110926.
39. Hirano T. Clinical significance of small dense low-density lipoprotein cholesterol measurement in type 2 diabetes. *J Diabetes Investig*. 2025;16:370–383. https://doi.org/10.1111/jdi.14398.
40. Jones DR, Schmidt RJ, Pickard RT, Foxworthy PS, Eacho PI. Estrogen receptor-mediated repression of human hepatic lipase gene transcription. *J Lipid Res*. 2002; 43:383–391.
41. Masuda R, Wist J, Lodge S, Kimhofer T, Hunter M, Hui J, et al. Plasma lipoprotein subclass variation in middle-aged and older adults: sex-stratified distributions and associations with health status and cardiometabolic risk factors. *J Clin Lipidol*. 2023; 17:677–687. https://doi.org/10.1016/j.jacl.2023.06.004.
42. Wang Q, Ferreira DLS, Nelson SM, Sattar N, Ala-Korpela M, Lawlor DA. Metabolic characterization of menopause: cross-sectional and longitudinal evidence. *BMC Med*. 2018;16:17. https://doi.org/10.1186/s12916-018-1008-8.
43. Shoji T, Emoto M, Kawagishi T, Kimoto E, Yamada A, Tabata T, et al. Atherogenic lipoprotein changes in diabetic nephropathy. *Atherosclerosis*. 2001;156:425–433. https://doi.org/10.1016/S0021-9150(00)00673-0.
44. Carr MC, Hokanson JE, Zambon A, Deeb SS, Barrett PH, Purnell JQ, et al. The contribution of intraabdominal fat to gender differences in hepatic lipase activity and low/high density lipoprotein heterogeneity. *J Clin Endocrinol Metab*. 2001;86: 2831–2837. https://doi.org/10.1210/jcem.86.6.7586.
45. Tabara Y, Arai H, Hirao Y, Takahashi Y, Setoh K, Kawaguchi T, et al. Different inverse association of large high-density lipoprotein subclasses with exacerbation of insulin resistance and incidence of type 2 diabetes: the Nagahama study. *Diabetes Res Clin Pract*. 2017;127:123–131. https://doi.org/10.1016/j.diabres.2017.03.018.
46. Joshi R, Wannamethee G, Engmann J, et al. Establishing reference intervals for triglyceride-containing lipoprotein subfraction metabolites measured using nuclear magnetic resonance spectroscopy in a UK population. *Ann Clin Biochem*. 2021;58: 47–53. https://doi.org/10.1177/0004563220961753.