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Original Article

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Lipoprotein Subfractions and Glucose Homeostasis in Prediabetes and Diabetes in Taiwan

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Aims: Prediabetes and diabetes are associated with increased insulin resistance and decreased insulin production, dyslipidemia, and increased cardiovascular disease (CVD) risk. Our goals were to assess lipoprotein subfractions using novel assays in such subjects.

Methods: Fasting normal, prediabetic, and diabetic Taiwanese men and women (n=2,049) had their serum glucose, glycosylated hemoglobin, insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), HDL3-C, apolipoprotein E-HDL-C, direct low-density lipoprotein cholesterol (LDL-C), small dense LDL-C (sdLDL-C), LDL-TG, and remnant lipoprotein cholesterol (RLP-C) levels measured using novel assays. HDL2-C, LDL-C, and large-buoyant LDL-C (lbLDL-C) were calculated.

Results: Prediabetic male and female subjects had significantly higher levels of TG, RLP-C, sdLDL-C, the sdLDL-C/LDL-C ratio, and LDL-TG than normal subjects, and statin treatment abolished this effect in men, but not in women. Diabetic male and female subjects had significantly higher TG and sdLDL-C/LDL-C ratios, and significantly lower levels of HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, as did prediabetic women. Median direct LDL-C levels were >100 mg/dL in all groups, even in those receiving statin therapy. Calculated LDL-C significantly underestimated direct LDL-C by >10% in diabetic subjects.

Conclusions: Our data indicate that prediabetic subjects were more likely to have significantly elevated RLP-C, sdLDL-C, and LDL-TG, while diabetic subjects were more likely to have significantly decreased HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, and calculated LDL-C significantly underestimated their direct LDL-C. In our view, direct LDL-C and sdLDL-C should be measured and optimized in both diabetic and prediabetic subjects to reduce CVD risk.

Key words: Low-density lipoprotein triglyceride, Small dense low-density lipoprotein cholesterol, Type 2 diabetes mellitus, Prediabetes, Lipid-lowering medication

Introduction

Diabetes mellitus is a major risk factor for cardiovascular disease (CVD), and is associated with dyslipidemia characterized by increased serum levels of triglycerides (TG), remnant lipoprotein cholesterol (RLP-C), and small dense low-density lipoproteins (sdLDL), and decreased levels of high-density lipoprotein cholesterol (HDL-C)[1-4]. Subjects with prediabetes are also at increased CVD risk, and often have dyslipidemia[5].

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Significant CVD risk factors in patients with diabetes include hypertension, smoking, increased levels of serum glucose and LDL-C, and decreased levels of HDL-C[6]. Lowering LDL-C levels with statin therapy has been associated with significant reductions in CVD events in patients with diabetes[7-11].

In the United States, it has been recommended that all patients with established CVD and diabetes over the age of 40 years with LDL-C levels >70 mg/dL, an LDL-C value ≥190 mg/dL, or a ten-year CVD risk ≥7.5% be placed on statin therapy in addition to lifestyle modification in order to achieve a significant LDL-C reduction[12-14]. More recently, it has been suggested that in addition to statins, the use of ezetimibe, and/or proprotein convertase subtilisin kexin 9 inhibitors can be considered to reduce LDL-C levels to <70 mg/dL in CVD patients and <100 mg/dL in high-risk patients including patients with diabetes[15, 16]. In the United States, there are no recommendations with regard to TG targets[12-16]. In Taiwan, current recommendations with regard to LDL-C targets of therapy are the same as in the United States, but it was also recommended that TG levels be lowered to <150 mg/dL[17, 18]. In Japan, it was recommended that CVD patients have their LDL-C values lowered to <100 mg/dL, and <120 mg/dL for diabetics, and for both groups to get TG levels lowered to <150 mg/dL[19]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, it was documented that diabetic subjects on statin therapy did not get additional benefit from the addition of fenofibrate therapy, unless their TG levels were >204 mg/dL and their HDL-C levels were <35 mg/dL. This latter group got a 28% risk reduction when fenofibrate was added to statin therapy as compared to placebo therapy[20].

It has long been known that hypertriglyceridemia is associated with decreased HDL-C values, as well as increased levels of sdLDL-C[21-23]. This latter parameter can now be readily measured with an automated assay[24]. In addition, it has been reported that elevated levels of RLP-C, sdLDL-C, and LDL-TG, and decreased levels of HDL-C and its subfractions have been associated with increased CVD risk[21-33]. However, these new assays have not been applied to a large diabetic and prediabetic population, especially in an Asian population.

Aim

Our purpose in the present study was to evaluate potential differences in the levels of RLP-C, direct LDL-C, large-buoyant LDL-C (lbLDL-C), sdLDL-C, HDL-C, HDL3-C, HDL2-C, and apoE-HDL-C among individuals with type 2 diabetes, prediabetes, or normal glucose tolerance using novel automated assays. Another goal of this investigation was to examine relationships between lipoprotein subfractions and measures of glucose homeostasis, including insulin, and measures of insulin resistance and production in normal, prediabetic, and diabetic subjects in a large Asian population.

Methods

Our study population consisted of 2,049 men and women living in Yi-lan County in northern Taiwan. Residents of this province are native to the island of Taiwan and are not recent immigrants from mainland China or other parts of Asia. All subjects agreed to participate in this study using a standard study protocol and informed consent approved by the research committees of Luodong Poh-ai Hospital, Luodong, Taiwan and the School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan. (M2000-2350).

We recruited normal, prediabetic, and diabetic subjects from participants after testing and participation in a standard health examination as previously described[34]. Subjects were classified as normal if their fasting serum glucose value was <100 mg/dL, as prediabetic if their value was in the 100−125 mg/dL range, and as diabetic if their value was >125 mg/dL using the standard criteria. In order to increase our diabetic subjects, subjects with diabetes were also recruited from a clinic at Luodong Poh-ai Hospital, and were required to have a history of diabetes without any change in treatment including medications for at least 6 months. All diabetic patients received standardized therapies consistent with national Taiwanese, American Diabetes Association and European Association for the Study of Diabetes guidelines. All participants were classified as being obese if their body mass index (BMI) was ≥27 kg/m² (Taiwanese criteria), or in some analyses (see **Supplemental Tables**) as ≥25 kg/m² (Japanese criteria)[35-37].

Subjects being treated for thyroid disease, or those with laboratory evidence of liver disease (transaminase value > three times the upper limits of normal), or kidney disease (creatinine >2.0 mg/dL), or those receiving insulin therapy were excluded from the study. Among the participants, 667 were in the normal group, 345 were in the prediabetic group, and 1,037 were in the diabetic group. In all subjects, a standard history about health status and medication use was obtained, and a physical examination was carried out including measurements of height, weight, and blood pressure. Subjects with a significant history of CVD were excluded from this analysis.

Blood samples were collected from all participants after an overnight fast of 12 hours or more. Serum

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Table 1. Characteristics of all male subjects ($n=1030$) *

Variable	NGT $n=277$	PreDM $n=200$	DM $n=553$	*P* value NGT vs PreDM	*P* value PreDM vs DM	*P* value DM vs NGT
Age, year	55.8 (20.3)	60.6 (18.6)	61.5 (14.6)	0.002	0.098	0.000
BMI, kg/m^2	24.2 (4.2)	25.3 (3.9)	26.1 (4.8)	0.001	0.001	0.000
Obesity Prevalence	50 (18.1%) **	53 (26.5%) **	217 (39.2%) **	0.001	0.001	0.000
Systolic BP, mmHg	123.0 (16.8)	128.0 (21.0)	130.0 (14.0)	0.004	0.738	0.002
Diastolic BP, mmHg	75.0 (13.8)	76.0 (16.0)	70.0 (10.0)	0.022	0.073	0.471
Fasting Glucose, mg/dL	93.0 (8.0)	105.0 (9.0)	133.0 (40.0)	0.000	0.000	0.000
HbA1c, %	5.5 (0.4)	5.8 (0.4)	6.9 (1.3)	0.000	0.000	0.000
Insulin,	8.0 (1.5)	10.6 (21.2)	10.7 (10.4)	0.000	0.823	0.000
HOMA-IR	1.8 (1.7)	2.8 (2.2)	3.5 (3.6)	0.000	0.000	0.000
HOMA-β	100.4 (90.4)	86.5 (58.7)	58.9 (65.8)	0.018	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	192.0 (55.0)	189.5 (43.3)	171.0 (39.2)	0.507	0.000	0.000
Triglycerides, mg/dL	103.0 (75.0)	120.0 (87.0)	118.0 (94.0)	0.002	0.888	0.000
RLP-C, mg/dL	6.3 (7.3)	8.7 (10.7)	6.3 (9.1)	0.001	0.001	0.984
LDL-C, mg/dL	113.3 (46.7)	111.8 (43.7)	106.4 (32.7)	0.880	0.032	0.008
calculated LDL-C, mg/dL	115.2 (51.1)	109.4 (43.8)	93.2 (35.7)	0.176	0.000	0.000
sdLDL-C, mg/dL	29.5 (22.2)	34.5 (25.0)	32.7 (20.4)	0.018	0.251	0.052
sdLDL-C/LDL-C ratio	0.260 (0.111)	0.305 (0.150)	0.299 (0.153)	0.000	0.896	0.000
lbLDL-C, mg/dL	80.1 (34.1)	78.0 (33.8)	73.2 (27.0)	0.094	0.028	0.000
LDL-TG, mg/dL	22.2 (11.0)	23.3 (10.1)	19.4 (7.7)	0.006	0.000	0.000
Non-HDL-C, mg/dL	140.7 (54.8)	138.7 (41.6)	122.7 (38.1)	0.945	0.000	0.000
HDL-C, mg/dL	51.3 (17.2)	50.3 (16.1)	46.0 (13.5)	0.460	0.000	0.000
HDL_2-C, mg/dL	26.9 (13.3)	27.0 (10.0)	25.1 (8.1)	0.447	0.069	0.005
HDL_3-C, mg/dL	22.8 (5.1)	22.8 (5.2)	20.5 (5.2)	0.784	0.000	0.000
ApoE-HDL, mg/dL	4.6 (2.2)	4.7 (2.0)	3.9 (1.7)	0.879	0.000	0.000

* Data are expressed as median (interquartile range).
** Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

glucose was measured using the hexokinase method, glycosylated hemoglobin using a turbidimetric inhibition immunoassay as previously described[34]. Insulin levels were measured by chemiluminescence assay on a Siemens Centaur automated platform (Siemens Healthineers, Germany) with intra- and inter-assay coefficients of variation (CVs) of < 5%. Serum creatinine, liver transaminases, TC, TG, HDL-C, HDL3-C, apoE-HDL-C, direct LDL-C, sdLDL-C, LDL-TG, and RLP-C were measured by automated standardized enzymatic analysis on a Cobas C501 analyzer (Roche Diagnostics, Germany). The specialized lipid assay kits were provided by the Denka-Seiken Corporation (Tokyo, Japan) as previously described[24, 31, 32, 38-43]. All specialized lipid assays had within and between run CVs were < 6.0%, and in most cases < 3.0%. Homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of insulin production (HOMA-β) were calculated from glucose and insulin levels using the following formulas: $HOMA_\beta$ = [(insulin in μU/mL × 360)/(glucose in mg/dL − 63)] %), and $HOMA_{IR}$ = [glucose in mg/dL × (insulin in μU/mL)/405)][44, 45]. lbLDL-C were calculated by subtracting sdLDL-C from direct LDL-C. HDL2-C were calculated by subtracting HDL3-C from HDL-C. LDL-C was calculated using the Friedewald formula by subtracting the sum of HDL-C and TG/5 from TC.

Data are presented as the median values with inter-quartile ranges since many variables were not normally distributed. All statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY). Mann−Whitney *U* testing was used to assess the sta-

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Table 2. Characteristics of all female subjects ($n=1019$)*

Variable	NGT $n=390$	PreDM $n=145$	DM $n=484$	*P* value		
				NGT vs PreDM	PreDM vs DM	DM vs NGT
Age, year	51.7 (16.4)	61.5 (18.8)	63.7 (12.3)	0.000	0.018	0.000
BMI, kg/m^2	22.8 (4.0)	23.8 (4.6)	25.5 (5.0)	0.001	0.000	0.000
Obesity Prevalence	36 (9.2%)**	31 (21.4%)**	172 (35.5%)**	0.001	0.000	0.000
Systolic BP, mmHg	118.0 (19.0)	123.0 (16.0)	130.0 (14.0)	0.003	0.000	0.000
Diastolic BP, mmHg	69.0 (14.0)	71.0 (14.3)	70.0 (10.0)	0.028	0.076	0.000
Fasting Glucose, mg/dL	90.0 (9.0)	105.0 (11.0)	132.0 (41.0)	0.000	0.000	0.000
HbA1c, %	5.5 (0.4)	5.9 (0.5)	7.0 (1.4)	0.000	0.000	0.000
Insulin,	8.3 (5.8)	12.7 (8.3)	13.2 (10.1)	0.000	0.251	0.000
HOMA-IR	1.8 (1.3)	3.3 (2.4)	4.3 (4.0)	0.000	0.000	0.000
HOMA-β	113.1 (76.4)	97.7 (67.8)	66.1 (68.0)	0.004	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	197.0 (48.8)	194.0 (42.0)	175.0 (36.3)	0.254	0.000	0.000
Triglycerides, mg/dL	86.5 (58.8)	116.0 (94.0)	119.0 (82.3)	0.000	0.983	0.000
RLP-C, mg/dL	5.3 (4.7)	7.9 (9.8)	6.2 (7.6)	0.000	0.000	0.000
LDL-C, mg/dL	117.0 (39.6)	114.3 (42.7)	106.6 (35.5)	0.448	0.007	0.000
calculated LDL-C, mg/dL	116.7 (42.9)	112.3 (42.1)	95.1 (34.7)	0.098	0.000	0.000
sdLDL-C, mg/dL	27.3 (17.1)	33.5 (21.4)	31.5 (19.6)	0.000	0.165	0.000
sdLDL-C/LDL-C ratio	0.231 (0.085)	0.287 (0.127)	0.290 (0.129)	0.000	0.813	0.000
lbLDL-C, mg/dL	87.9 (28.0)	80.6 (29.3)	74.5 (26.5)	0.001	0.002	0.000
LDL-TG, mg/dL	21.2 (10.0)	25.2 (10.5)	20.9 (8.3)	0.000	0.000	0.857
Non-HDL-C, mg/dL	134.4 (48.1)	139.3 (41.7)	121.6 (36.3)	0.335	0.000	0.000
HDL-C, mg/dL	59.2 (18.4)	52.2 (17.9)	52.5 (15.8)	0.000	0.962	0.000
HDL_2-C, mg/dL	34.0 (14.7)	28.9 (11.8)	29.4 (11.0)	0.000	0.171	0.000
HDL_3-C, mg/dL	25.0 (4.7)	23.9 (5.4)	22.8 (5.6)	0.018	0.001	0.000
ApoE-HDL, mg/dL	5.7 (2.3)	5.0 (2.0)	4.7 (1.9)	0.000	0.020	0.000

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, non HDL cholesterol;

tistical significance of differences for assessed variables between groups. Pearson's correlation coefficients were used for assessing the significance of correlations between variables. A *P* value of <0.05 was considered statistically significant.

Results

Data on all male ($n=1,030$) and female ($n=1,019$) participants are shown in **Tables 1** and **2**, respectively. Since this study focused on lipoprotein subfractions, data on male ($n=605$) and female ($n=622$) subjects off lipid-lowering medications are shown in **Table 3** and **4**, respectively, while data on men ($n=347$) and women ($n=339$) on statin therapy are shown in **Tables 5** and **6**, respectively. In addition, we tabulated relative percentage differences between normal, prediabetic, and diabetic male and female subjects for all lipoprotein subfractions in all subjects, those off statins, and in those on statin therapy in **Figs.1**, **2**, and **3**, respectively. In addition, we have analyzed the effects of obesity classified as ≥ 27 kg/m^2 using the Taiwanese criteria in normal prediabetic and diabetic subgroups for men in **Table 7**, and for women in **Table 8**. Comparisons of normal, prediabetic, and diabetic men and women with and without obesity classified as ≥ 25 kg/m^2 using Japanese criteria are shown in **Supplemental Tables 1** and **2**. Comparison of variables between participants with and without statin use are shown in **Supplemental Table 3–5** (normal group in **Supplemental Table 3**, prediabetic group in **Supplemental Table 4**, and DM group in **Supplemental Table 5**).

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Table 3. Characteristics of male subjects not on lipid medications ($n=605$)*

Variable	NGT $n=207$	PreDM $n=117$	DM $n=281$	*P* value		
				NGT vs PreDM	PreDM vs DM	DM vs NGT
Age, year	52.2 (18.3)	54.5 (18.5)	61.9 (13.4)	0.017	0.000	0.000
BMI, kg/m^2	23.9 (4.1)	25.3 (4.0)	25.4 (4.7)	0.000	0.710	0.000
Obesity Prevalence	36 (17.4%)**	36 (30.8%)**	94 (33.5%)**	0.000	0.710	0.000
Systolic BP, mmHg	122.0 (15.8)	130.0 (22.0)	130.0 (14.0)	0.001	0.579	0.021
Diastolic BP, mmHg	74.0 (13.0)	77.0 (17.0)	76.0 (10.0)	0.006	0.280	0.187
Fasting Glucose, mg/dL	92.0 (7.5)	105.0 (10.0)	134.0 (35.0)	0.000	0.000	0.000
HbA1c, %	5.5 (0.4)	5.8 (0.5)	6.9 (1.1)	0.000	0.000	0.000
Insulin,	7.9 (7.4)	10.6 (8.9)	10.5 (10.7)	0.000	0.934	0.000
HOMA-IR	1.8 (1.6)	2.7 (2.3)	3.3 (3.7)	0.000	0.006	0.000
HOMA-β	99.5 (96.2)	85.1 (63.5)	55.2 (61.7)	0.008	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	196.1 (50.5)	192.0 (32.0)	171.0 (33.0)	0.388	0.000	0.000
Triglycerides, mg/dL	103.0 (79.5)	133.0 (99.0)	116.0 (91.0)	0.006	0.316	0.013
RLP-C, mg/dL	6.3 (8.2)	10.1 (11.6)	5.6 (8.0)	0.001	0.000	0.061
LDL-C, mg/dL	116.7 (44.8)	115.5 (40.9)	107.2 (30.1)	0.686	0.003	0.000
calculated LDL-C, mg/dL	117.7 (47.3)	113.5 (39.9)	94.1 (31.0)	0.103	0.000	0.000
sdLDL-C, mg/dL	30.7 (22.9)	34.9 (26.1)	31.8 (18.8)	0.075	0.032	0.957
sdLDL-C/LDL-C ratio	0.256 (0.118)	0.310 (0.164)	0.288 (0.139)	0.004	0.386	0.003
lbLDL-C, mg/dL	84.9 (33.0)	79.7 (32.5)	74.6 (25.2)	0.115	0.021	0.000
LDL-TG, mg/dL	22.1 (11.3)	23.4 (10.9)	18.1 (6.6)	0.026	0.000	0.000
Non HDL-C, mg/dL	142.9 (52.2)	141.6 (33.2)	122.8 (30.9)	0.815	0.000	0.000
HDL-C, mg/dL	51.6 (18.1)	51.4 (18.0)	46.0 (13.6)	0.551	0.003	0.000
HDL_2-C, mg/dL	27.6 (13.0)	26.3 (12.4)	25.2 (8.3)	0.448	0.238	0.015
HDL_3-C, mg/dL	23.0 (5.8)	22.9 (5.5)	20.5 (5.1)	0.899	0.000	0.000
ApoE-HDL, mg/dL	4.6 (2.1)	4.8 (2.1)	3.7 (1.5)	0.857	0.000	0.000

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

Correlations between variables for all subjects, men and women are shown in **Supplemental Tables 6**, **7**, and **8**.

For all subjects and for those not receiving or receiving statin therapy, the median BMI, obesity prevalence, systolic blood pressure, serum glucose, HbA1c, serum insulin, and calculated insulin resistance ($HOMA_{IR}$) were all significantly higher in prediabetic and diabetic subjects than in normal subjects. In contrast, median calculated insulin production ($HOMA_{\beta}$) values were significantly lower in prediabetic and diabetic subjects than in normal, especially in those with diabetes (see **Tables 1-6**). Interestingly serum insulin levels were not significantly different between prediabetic and diabetic subjects in all categories, but there were significantly higher $HOMA_{IR}$ values and significantly lower $HOMA_{\beta}$ values in diabetic subjects than in normal subjects.

In all male prediabetic subjects, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects (see **Table 1**). In male prediabetics not on statin therapy, TG, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects (see **Table 3**). In male prediabetics on statin therapy, all these significant differences were abolished (see **Table 5**). In all female prediabetic subjects, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects, while lbLDL-C, HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normals (see **Table 2**). In female prediabetic subjects off statin

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Table 4. Characteristics of female subjects not on lipid medications ($n=622$)*

Variable	NGT $n=324$	PreDM $n=90$	DM $n=208$	*P* value		
				NGT vs PreDM	PreDM vs DM	DM vs NGT
Age, year	49.3 (12.9)	54.7 (19.2)	63.6 (11.9)	0.000	0.000	0.000
BMI, kg/m^2	22.5 (4.0)	24.1 (5.2)	24.8 (4.8)	0.000	0.285	0.000
Obesity Prevalence	25 (7.7%)**	23 (25.6%)**	57 (27.4%)**	0.000	0.285	0.000
Systolic BP, mmHg	117.0 (19.0)	120.0 (17.0)	130.0 (19.5)	0.025	0.001	0.000
Diastolic BP, mmHg	68.0 (14.0)	70.5 (11.8)	70.0 (10.0)	0.086	0.056	0.001
Fasting Glucose, mg/dL	89.5 (8.0)	105.0 (11.0)	132.0 (39.5)	0.000	0.000	0.000
HbA1c, %	5.4 (0.4)	5.8 (0.7)	7.0 (1.2)	0.000	0.000	0.000
Insulin,	7.9 (5.6)	11.9 (8.2)	12.0 (9.4)	0.000	0.669	0.000
HOMA-IR	1.8 (1.3)	3.2 (2.2)	4.0 (3.6)	0.000	0.002	0.000
HOMA-β	110.7 (76.0)	95.7 (64.5)	60.9 (60.0)	0.003	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	198.0 (47.3)	194.5 (38.5)	178.0 (31.1)	0.678	0.000	0.000
Triglycerides, mg/dL	81.0 (57.5)	106.5 (82.8)	118.0 (75.0)	0.000	0.395	0.000
RLP-C, mg/dL	4.8 (4.2)	7.0 (8.4)	5.3 (6.1)	0.000	0.001	0.089
LDL-C, mg/dL	117.7 (39.2)	118.1 (39.5)	108.4 (29.7)	0.934	0.003	0.000
calculated LDL-C, mg/dL	117.4 (41.1)	113.5 (36.2)	99.0 (28.1)	0.521	0.000	0.000
sdLDL-C, mg/dL	26.5 (16.8)	32.5 (22.5)	29.4 (19.9)	0.001	0.179	0.010
sdLDL-C/LDL-C ratio	0.226 (0.081)	0.272 (0.103)	0.272 (0.124)	0.000	0.701	0.000
lbLDL-C, mg/dL	89.8 (27.4)	84.4 (22.7)	76.4 (24.1)	0.115	0.000	0.000
LDL-TG, mg/dL	20.1 (9.9)	23.3 (10.6)	19.3 (7.9)	0.000	0.000	0.194
Non HDL-C, mg/dL	133.4 (48.1)	139.7 (38.8)	124.4 (33.5)	0.216	0.000	0.000
HDL-C, mg/dL	59.9 (18.8)	53.6 (16.7)	50.3 (17.2)	0.000	0.061	0.000
HDL$_2$-C, mg/dL	34.7 (16.1)	29.8 (13.7)	28.4 (11.8)	0.000	0.479	0.000
HDL$_3$-C, mg/dL	25.1 (4.7)	23.9 (5.4)	22.2 (5.2)	0.186	0.000	0.000
ApoE-HDL, mg/dL	5.7 (2.3)	5.2 (2.3)	4.4 (2.0)	0.001	0.000	0.000

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

therapy, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normals, while HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normal subjects (see **Table 4**). In female prediabetic subjects on statin therapy, TG, RLP-C, and sdLDL-C/LDL-C ratio values were all significantly higher than in normal, while HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normal (see **Table 6**).

In all male diabetic subjects, TG, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects, while direct LDL-C, calculated LDL-C, non-HDL-C, HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C were all significantly lower than in normal subjects (see **Table 1**). In diabetic men not on statin therapy, with very similar differences being observed in diabetic men not on statin therapy versus normal subjects (see **Table 5**). In all female diabetics, TG, RLP-C, sdLDL-C, and sdLDL-C/LDL-C ratio values were all significantly higher than in nortmal subjects, while lbLDL-C, HDL-C, and apoE-HDL-C were all significantly lower than in normal subjects. In all female diabetics off statin therapy, TG, sdLDL-C, and sdLDL-C/LDL-C ratio values were all significantly higher than in normal subjects, while direct LDL-C, calculated LDL-C, lbLDL-C, non-HDL-C, HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C were all significantly lower than in normal subjects. Interestingly, median direct LDL-C values in male and female diabetic subjects in all three categories ranged from 104.1−108.4 mg/dL, whereas for calculated LDL-C, these values ranged from 90.7−99.0 mg/dl, with an average

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Table 5. Characteristics of male subjects on statins ($n=347$)*

Variable	NGT $n=62$	PreDM $n=79$	DM $n=206$	*P* value		
				NGT vs PreDM	PreDM vs DM	DM vs NGT
Age, year	66.0 (16.2)	66.0 (12.7)	62.4 (15.2)	0.911	0.030	0.089
BMI, kg/m^2	24.7 (3.4)	25.0 (4.1)	26.6 (4.9)	0.923	0.000	0.001
Obesity Prevalence	14 (22.6%)**	16 (20.3%)**	88 (42.7%)**	0.923	0.001	0.001
Systolic BP, mmHg	130.0 (15.3)	127.0 (12.0)	130.0 (10.0)	0.630	0.797	0.694
Diastolic BP, mmHg	75.0 (10.8)	75.0 (11.0)	70.0 (10.0)	0.742	0.878	0.447
Fasting Glucose, mg/dL	94.0 (7.0)	106.0 (8.5)	132.0 (39.8)	0.000	0.000	0.000
HbA1c, %	5.6 (0.3)	5.9 (0.4)	6.8 (1.4)	0.000	0.000	0.000
Insulin,	8.5 (6.8)	11.2 (8.0)	10.4 (7.9)	0.000	0.369	0.000
HOMA-IR	1.9 (1.5)	3.0 (2.1)	3.5 (3.0)	0.000	0.081	0.000
HOMA-β	104.0 (68.5)	90.4 (51.9)	60.0 (56.7)	0.669	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	175.5 (57.2)	184.0 (56.0)	168.0 (50.8)	0.437	0.006	0.141
Triglycerides, mg/dL	100.5 (47.3)	111.0 (69.0)	118.0 (88.3)	0.119	0.478	0.014
RLP-C, mg/dL	5.7 (5.6)	7.4 (8.3)	7.3 (9.4)	0.066	0.779	0.096
LDL-C, mg/dL	102.1 (46.0)	106.7 (48.8)	104.7 (40.9)	0.540	0.881	0.451
calculated LDL-C, mg/dL	100.6 (51.9)	102.4 (46.3)	92.0 (41.7)	0.628	0.002	0.029
sdLDL-C, mg/dL	27.5 (15.0)	33.4 (22.4)	33.2 (21.0)	0.070	0.847	0.016
sdLDL-C/LDL-C ratio	0.265 (0.070)	0.288 (0.121)	0.304 (0.140)	0.054	0.486	0.003
lbLDL-C, mg/dL	76.0 (32.7)	73.8 (31.0)	72.4 (26.8)	0.639	0.557	0.389
LDL-TG, mg/dL	22.0 (8.2)	22.9 (8.8)	20.0 (8.1)	0.094	0.000	0.116
Non HDL-C, mg/dL	122.9 (51.7)	131.1 (50.3)	119.5 (44.6)	0.260	0.013	0.404
HDL-C, mg/dL	49.9 (16.0)	49.4 (13.8)	46.8 (14.1)	0.651	0.187	0.046
HDL$_2$-C, mg/dL	26.4 (12.9)	27.1 (7.9)	25.4 (8.4)	0.648	0.430	0.201
HDL$_3$-C, mg/dL	22.8 (4.2)	22.5 (5.3)	20.9 (5.3)	0.975	0.006	0.009
ApoE-HDL, mg/dL	4.5 (2.5)	4.6 (1.9)	4.1 (1.8)	0.884	0.011	0.009

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

underestimation of 11.5% ($p<0.001$).

For all groups, we have tabulated relative percent differences between normal, prediabetic, and diabetic male and female subjects for all lipid and lipoprotein subfractions (see **Figs.1**, **2**, and **3**). A number of different patterns emerged. One pattern is that prediabetic subjects had the greatest increases in RLP-C, sdLDL-C, and LDL-TG values, especially in female subjects, as compared with normal subjects. Another pattern that emerged is that diabetic subjects had the greatest decreases in HDL-C and its subfractions as compared with normal, especially in men. In women, significant decreases in HDL-C and its subfractions were observed in prediabetic subjects as compared with normal; however, this was not the case for prediabetic men. A final pattern that emerged was that calculated LDL-C significantly underestimated direct LDL-C values in diabetic male and female subjects, with less discrepancy observed in normal and prediabetic subjects.

We examined the effects of obesity classified as having a BMI >27 kg/m^2 versus being non-obese in normal, prediabetic, and diabetic men and women. The data are shown in **Tables 7** and **8**. In normal men, being obese resulted in significantly higher systolic blood pressure, insulin, HOMA$_{IR}$, HOMA$_\beta$, TG, sdLDL-C, sdLDL-C/LDL-C ratio, non-HDL-C, and LDL-TG values, and significantly lower HDL-C, HDL2-C, and apoE-HDL-C as compared with non-obese normal subjects (see **Table 7**). In normal women, being obese resulted in the same differences except that TG and non-HDL-C levels were not significantly higher, but HDL3-C was significantly lower as compared with

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Table 6. Characteristics of female subjects on statins ($n=339$)*

Variable	NGT $n=60$	PreDM $n=52$	DM $n=227$	*P* value		
				NGT vs PreDM	PreDM vs DM	DM vs NGT
Age, year	69.5 (13.0)	68.0 (12.8)	64.3 (13.1)	0.972	0.012	0.011
BMI, kg/m^2	24.0 (4.1)	23.5 (4.5)	26.2 (5.4)	0.297	0.000	0.000
Obesity Prevalence	10 (16.7%)**	8 (15.4%)**	94 (41.4%)**	0.297	0.001	0.001
Systolic BP, mmHg	129.5 (18.3)	130.0 (10.0)	130.0 (10.0)	0.793	0.840	0.814
Diastolic BP, mmHg	76.0 (10.5)	77.0 (12.0)	70.0 (10.0)	0.840	0.602	0.452
Fasting Glucose, mg/dL	92.0 (8.5)	104.5 (10.3)	131.0 (42.0)	0.000	0.000	0.000
HbA1c, %	5.6 (0.5)	5.9 (0.4)	6.9 (1.3)	0.001	0.000	0.000
Insulin,	10.1 (7.6)	13.4 (10.2)	13.7 (10.5)	0.009	0.738	0.000
HOMA-IR	2.3 (1.7)	3.4 (2.6)	4.6 (3.9)	0.000	0.005	0.000
HOMA-β	128.9 (85.5)	116.4 (75.1)	69.2 (72.7)	0.097	0.000	0.000
Lipids and Lipoproteins						
Total cholesterol, mg/dL	193.8 (56.0)	193.5 (54.5)	172.0 (41.0)	0.433	0.007	0.000
Triglycerides, mg/dL	107.6 (68.3)	131.5 (106.3)	120.0 (78.0)	0.003	0.038	0.162
RLP-C, mg/dL	7.4 (5.8)	9.5 (14.6)	6.8 (8.7)	0.012	0.003	0.809
LDL-C, mg/dL	112.5 (40.6)	110.0 (49.0)	104.1 (39.6)	0.733	0.490	0.142
calculated LDL-C, mg/dL	111.2 (52.1)	102.9 (55.1)	90.7 (35.4)	0.261	0.015	0.000
sdLDL-C, mg/dL	30.0 (17.2)	35.8 (21.4)	32.8 (16.9)	0.077	0.181	0.371
sdLDL-C/LDL-C ratio	0.278 (0.091)	0.330 (0.136)	0.301 (0.131)	0.003	0.255	0.007
lbLDL-C, mg/dL	81.7 (31.4)	72.2 (29.5)	71.7 (27.8)	0.067	0.926	0.012
LDL-TG, mg/dL	23.8 (6.1)	26.9 (10.1)	21.7 (8.6)	0.105	0.000	0.015
Non HDL-C, mg/dL	135.9 (53.9)	138.5 (54.9)	117.3 (36.8)	0.972	0.002	0.001
HDL-C, mg/dL	58.2 (15.4)	51.0 (12.6)	54.0 (13.9)	0.002	0.044	0.042
HDL_2-C, mg/dL	32.1 (11.1)	26.1 (9.1)	30.3 (10.2)	0.002	0.003	0.152
HDL_3-C, mg/dL	24.9 (3.9)	22.8 (4.9)	23.4 (5.3)	0.092	0.875	0.025
ApoE-HDL, mg/dL	5.8 (2.0)	4.9 (1.4)	5.0 (1.8)	0.007	0.606	0.003

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

normal subjects (see **Table 8**). In prediabetic men, being obese resulted in the same findings as for normal men, except that no significant differences with regard to HDL-C and its subfractions were noted as compared with non-obese prediabetic men. In prediabetic women, being obese resulted in only significantly higher systolic blood pressure, HbA1c, insulin, $HOMA_{IR}$, $HOMA_{\beta}$, but no other parameters, as compared with prediabetic, non-obese women (see **Table 8**). In diabetic men, being obese resulted in significantly higher insulin, $HOMA_{IR}$, $HOMA_{\beta}$, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, LDL-TG, lbLDL-C, non-HDL-C, and significantly lower levels of HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C, compared with non-obese diabetic men (see **Table 7**). In contrast, in diabetic women, being obese was only associated with significantly higher levels of insulin and $HOMA_{\beta}$, and significantly lower levels of HDL2-C, as compared with non-obese diabetic women (see **Table 8**). Surprisingly, in this analysis, the presence of obesity had little effect on fasting glucose levels, possibly because group selections by gender were based on this parameter. Similar effects of obesity using the ≥ 25 kg/m^2 criteria were observed in all of the above subgroups (see **Supplementary Tables 1** and **2**). It should also be noted that, as previously mentioned, the prevalence of obesity was significantly higher in prediabetic and diabetic men and women versus controls as shown in **Tables 1** and **2**.

We also examined the effects of statin use in normal men and women (see **Supplementary Table 3**), in prediabetic men and women (see **Supplementary Table 4**), and in diabetic men and women (see **Sup-**

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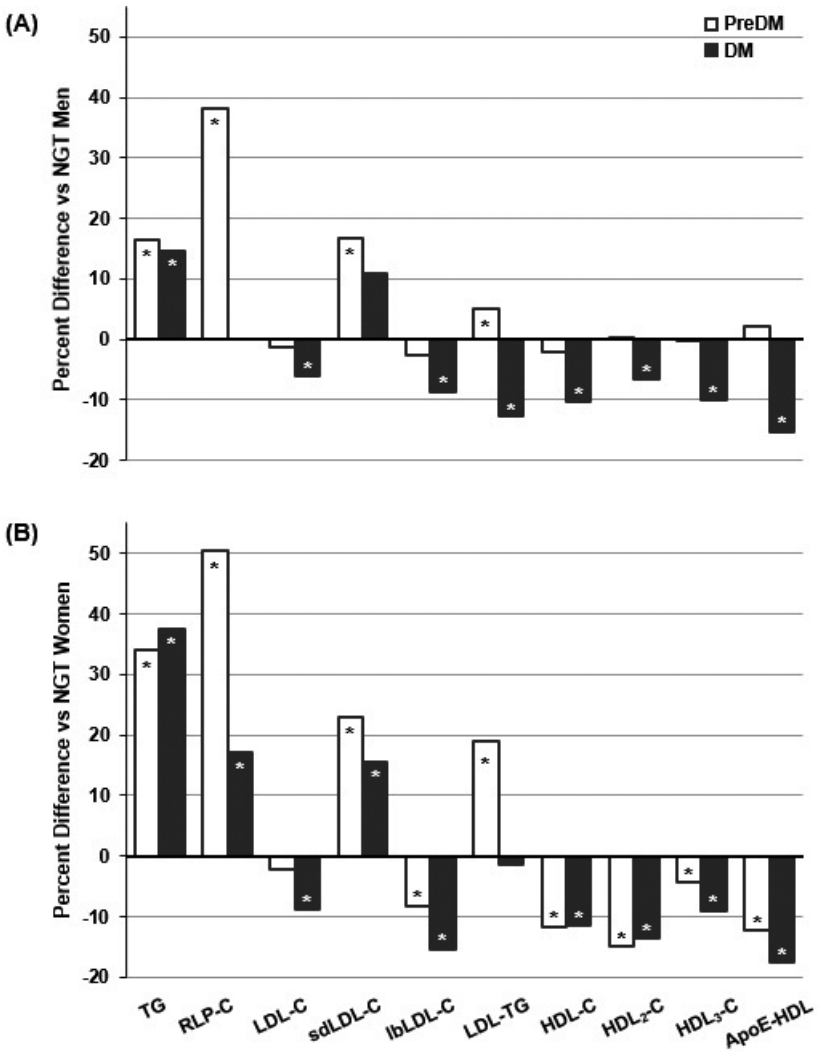

Fig. 1. (A) Percent differences of lipid variables in all male subjects with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. (B) Percent differences of lipid variables in all female subjects with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. Star sign (*) indicate $p < 0.05$

plementary Table 5). In normal men, statin use was significantly associated with being older, having a higher BMI, and having a higher prevalence of obesity as compared with non-users. In prediabetic men, statin use was significantly associated with being older and having lower RLP-C values than non-users. In diabetic men, statin use was significantly associated with higher BMI, obesity prevalence, LDL-TG, and apoE-HDL-C values as compared with non-users. In normal women, statin use was associated with significantly higher age, BMI, obesity prevalence, systolic blood pressure, diastolic blood pressure, glucose, HbA1c, insulin, HOMA$_{IR}$, TG, lbLDL-C, and sdLDL/LDL-C ratio as compared with non-users. In prediabetic women, statin use was significantly associated with higher age, systolic blood pressure, TG, RLP-C, sdLDL/LDL-C ratio, and LDL-TG as compared with non-users. In diabetic women, statin use was significantly associated with higher BMI, sdLDL/LDL-C ratio, LDL-TG, HDL-C, HDL3-C, and apoE-HDL-C as compared with non-users.

We have also examined correlations between parameters in men and women participating in this study (see Supplementary Tables 6, 7, and 8). We observed very strong correlations between TC, calculated LDL-C, direct LDL-C, sdLDL-C, and LDL-TG, and somewhat weaker correlations between TC and HDL3-C, HDL-C, apoE HDL-C, and RLP-C. The strongest

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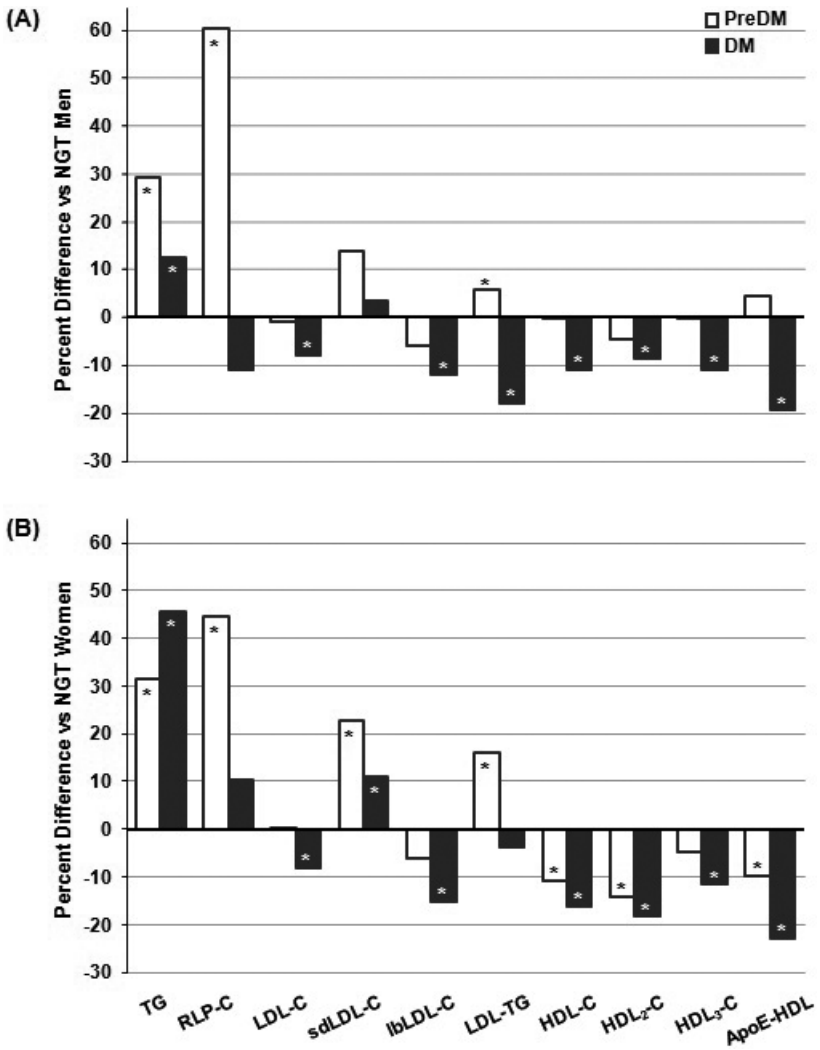

Fig. 2. (A) Percent differences of lipid variables in male subjects without lipid medication with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. (B) Percent differences of lipid variables in all female subjects without lipid medication with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. Star sign (*) indicate $p < 0.05$

positive correlations with TG levels were with RLP-C, LDL-TG, and sdLDL-C, as well as strong inverse correlation with HDL-C and somewhat weaker correlations with HDL3-C and apoE HDL-C. We also noted that insulin and $HOMA_{IR}$ values were significantly correlated with TG values, while $HOMA_{B}$ was modestly correlated with LDL-TG.

Discussion

In order to prevent CVD in prediabetic and diabetic subjects, not only glycemic control, but control of blood pressure and lipids and their subfractions are also important. Our focus in this study was to carefully examine lipids and lipoprotein subfractions using standard and novel markers in subjects with prediabetes and diabetes as compared with normal subjects in a large Asian population of over 2,000 individuals. In addition, we examined these parameters in both men and women, as well as in those who are off and on lipid-lowering medication. In addition, we related these parameters to markers of glucose homeostasis, namely fasting values of glucose, insulin, HbA1c, and calculated $HOMA_{IR}$ and $HOMA_{\beta}$. Our data reinforces the concept that both increased insulin resistance and decreased insulin production underlie the pathogene-

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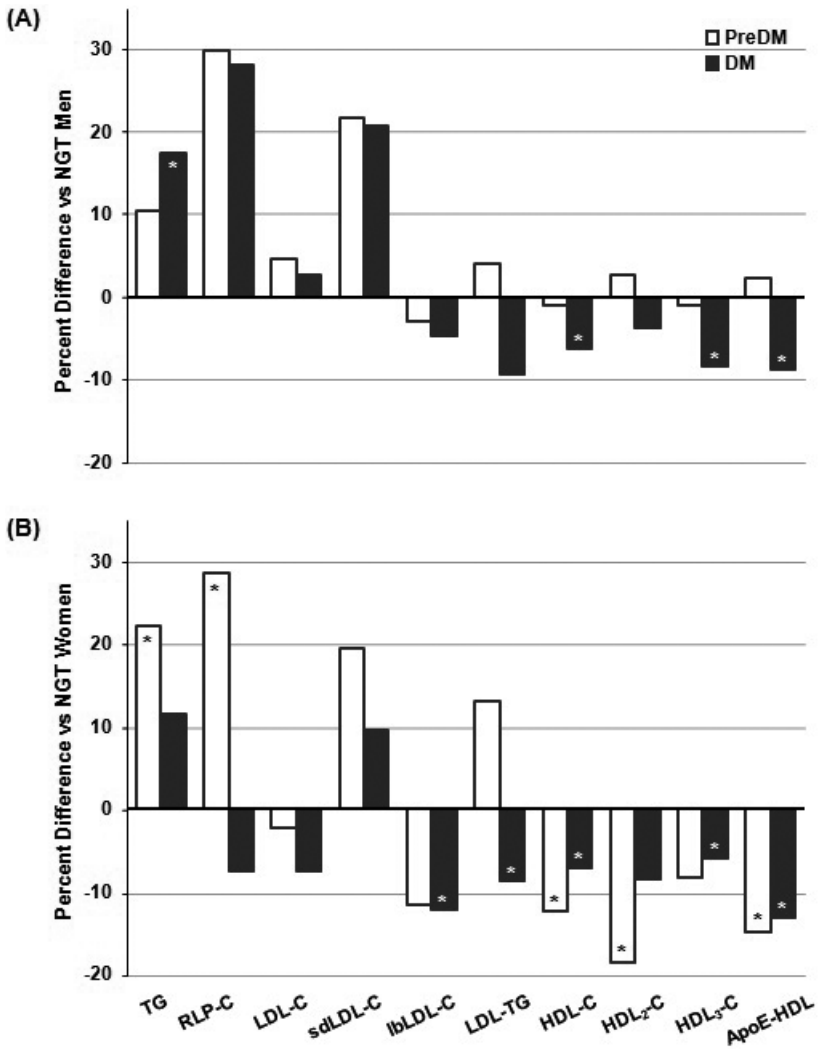

Fig. 3. (A) Percent differences of lipid variables in male subjects on statin treatment with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. (B) Percent differences of lipid variables in all female subjects on lipid medication with prediabetes (PreDM; white column) or diabetes (DM; black column) from non-diabetic. Star sign (*) indicate $p<0.05$

sis of prediabetes and the transition to diabetes, and that obesity plays an important role in this process. Recent studies using novel automated assays indicate that elevated levels of sdLDL-C and LDL-TG provide significant information about CVD risk above and beyond standard risk factors, and this may be the case for decreased levels of HDL subfractions and apoE HDL-C as well[27-33, 46]. However, to our knowledge, such new assays have not been applied to a relatively large population of male and female prediabetic and diabetic subjects.

It has long been known that diabetics have dyslipidemia with elevated TG, RLP-C, sdLDL-C, and decreased HDL-C values as compared to controls[1-4]. However, these older observations were made with a more manual cumbersome method of measuring RLP-C and gradient gel technology for assessing LDL particle size. In addition, more recently, it has been documented that diabetic subjects on statin therapy get additional benefit from the addition of fenofibrate if they have fasting TG values >204 mg/dL and HDL-C values <35 mg/dL[17, 19]. It is also known that statins can have beneficial effects not only on calculated LDL-C, but also on TG, RLP-C, direct LDL-C, sdLDL-C, and sdLDL-C[39]. While statins clearly have strikingly beneficial effects on CVD risk reduction in

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Table 7. Effects of Obesity Status (Taiwanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Men*

Variables	NGT			PreDM			DM		
	BMI < 27 n = 220	BMI ≧27 n = 50	P	BMI < 27 n = 140	BMI ≧27 n = 53	P	BMI < 27 n = 320	BMI ≧27 n = 217	P
Age, year	55.7 (20.7)	54.6 (19.4)	0.338	60.9 (17.9)	58.3 (20.7)	0.669	62.9 (14.9)	60.0 (13.8)	0.000
BMI, kg/m^2	23.5 (3.4)	29.0 (2.5)	0.000	24.2 (2.9)	28.7 (3.3)	0.000	24.1 (2.8)	29.3 (3.1)	0.000
Systolic BP, mmHg	122.0 (16.0)	128.0 (19.8)	0.004	127.0 (19.5)	131.0 (25.5)	0.026	130.0 (10.5)	130.0 (16.0)	0.929
Diastolic BP, mmHg	74.0 (14.8)	78.0 (13.8)	0.017	75.0 (15.0)	79.5 (15.0)	0.055	70.0 (10.0)	70.0 (10.0)	0.522
Fasting Glucose, mg/dL	92.0 (8.0)	93.0 (7.5)	0.222	104.0 (8.3)	105.0 (13.0)	0.196	133.0 (38.3)	135.0 (41.0)	0.291
HbA1c, %	5.5 (0.4)	5.6 (0.5)	0.140	5.8 (0.4)	5.8 (0.6)	0.289	6.8 (1.2)	7.1 (1.3)	0.008
Insulin,	7.0 (5.8)	13.6 (9.0)	0.000	10.0 (5.9)	17.1 (14.8)	0.000	8.8 (7.2)	14.7 (13.1)	0.000
HOMA-IR	1.6 (1.4)	3.1 (2.2)	0.000	2.6 (1.7)	4.6 (4.0)	0.000	2.8 (2.5)	4.9 (4.7)	0.000
HOMA-β	89.0 (70.5)	183.1 (116.2)	0.000	78.9 (49.1)	131.8 (106.6)	0.000	45.1 (47.7)	77.4 (73.9)	0.000
Lipids and Lipoproteins									
Total cholesterol, mg/dL	192.0 (53.5)	198.1 (65.1)	0.262	188.0 (44.3)	196.0 (37.0)	0.107	171.0 (38.3)	171.0 (43.2)	0.652
Triglycerides, mg/dL	99.0 (62.3)	144.5 (99.5)	0.000	111.5 (78.3)	147.0 (117.0)	0.046	110.0 (78.0)	134.0 (98.0)	0.000
RLP-C, mg/dL	6.0 (6.8)	10.1 (13.5)	0.405	7.4 (9.2)	11.8 (11.7)	0.132	5.6 (7.6)	8.0 (10.3)	0.000
LDL-C, mg/dL	111.4 (43.7)	116.8 (59.7)	0.087	108.5 (40.4)	120.5 (46.8)	0.057	106.3 (30.3)	108.8 (35.3)	0.507
calculated LDL-C, mg/dL	115.9 (50.7)	115.7 (48.0)	0.413	111.0 (44.5)	115.4 (41.1)	0.319	94.1 (31.4)	94.5 (37.8)	0.817
sdLDL-C, mg/dL	29.0 (20.5)	35.4 (35.0)	0.000	32.0 (20.7)	43.6 (26.3)	0.001	30.6 (18.8)	36.8 (22.6)	0.000
sdLDL-C/LDL-C ratio	0.256 (0.112)	0.301 (0.154)	0.001	0.289 (0.128)	0.327 (0.170)	0.008	0.2857 (0.137)	0.324 (0.193)	0.000
lbLDL-C, mg/dL	80.1 (34.1)	78.7 (39.1)	0.947	78.0 (31.6)	79.7 (36.7)	0.720	74.5 (26.2)	73.0 (29.6)	0.050
LDL-TG, mg/dL	21.8 (10.3)	25.4 (17.6)	0.000	22.4 (9.5)	27.3 (9.8)	0.003	18.8 (7.0)	20.7 (8.5)	0.001
Non-HDL-C, mg/dL	139.5 (52.8)	145.6 (58.9)	0.032	137.0 (42.5)	151.1 (39.3)	0.085	119.9 (36.7)	126.0 (36.7)	0.020
HDL-C, mg/dL	51.9 (17.4)	44.8 (16.1)	0.004	49.5 (16.4)	51.0 (15.4)	0.965	48.2 (13.9)	44.1 (11.4)	0.000
HDL$_2$-C, mg/dL	27.9 (13.2)	24.3 (10.8)	0.001	26.7 (9.2)	28.1 (10.8)	0.962	26.4 (9.5)	23.6 (6.9)	0.000
HDL$_3$-C, mg/dL	23.0 (5.5)	22.3 (5.0)	0.312	22.7 (4.9)	22.9 (6.0)	0.985	21.0 (5.1)	19.9 (4.9)	0.002
ApoE-HDL, mg/dL	4.7 (2.1)	4.2 (2.4)	0.030	4.7 (2.0)	4.7 (2.1)	0.968	4.0 (1.7)	3.6 (1.5)	0.000

*Obesity criteria based on Taiwanese criteria of < or ≥ 27 kg/m^2, and all data are expressed as median (interquartile range). The prevalence of obesity was 18.5%, 27.5%, and 40.4% in the NGT, prediabetic, and diabetic groups, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.

Table 8. Effects of Obesity Status (Taiwanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Women*

Variables	NGT			PreDM			DM		
	BMI < 27 n = 345	BMI ≧27 n = 36	P	BMI < 27 n = 107	BMI ≧27 n = 31	P	BMI < 27 n = 301	BMI ≧27 n = 172	P
Age, year	51.2 (16.5)	54.9 (23.6)	0.074	60.0 (18.8)	66.2 (18.8)	0.326	64.5 (12.5)	62.0 (14.0)	0.000
BMI, kg/m^2	22.4 (3.6)	28.7 (2.6)	0.000	22.8 (3.2)	28.6 (2.5)	0.000	23.8 (3.3)	29.2 (3.8)	0.000
Systolic BP, mmHg	117.5 (19.0)	120.0 (17.5)	0.014	122.0 (17.0)	127.5 (19.5)	0.001	130.0 (13.5)	128.0 (10.0)	0.078
Diastolic BP, mmHg	69.0 (14.0)	77.0 (13.5)	0.003	70.0 (13.0)	75.5 (14.3)	0.049	70.0 (10.0)	70.0 (10.0)	0.907
Fasting Glucose, mg/dL	90.0 (9.0)	90.5 (8.3)	0.642	105.0 (10.5)	105.0 (12.5)	0.262	131.0 (41.0)	133.0 (40.3)	0.129
HbA1c, %	5.4 (0.5)	5.6 (0.4)	0.550	5.9 (0.6)	6.0 (0.6)	0.039	6.9 (1.3)	7.0 (1.3)	0.138
Insulin,	8.0 (5.3)	11.3 (6.1)	0.000	11.3 (7.1)	18.4 (10.0)	0.001	10.9 (8.7)	16.8 (11.8)	0.008
HOMA-IR	1.8 (1.3)	2.5 (1.2)	0.000	2.9 (2.0)	4.8 (2.8)	0.005	3.6 (3.3)	5.6 (5.3)	0.005
HOMA-β	110.7 (72.6)	139.9 (97.9)	0.004	88.7 (62.0)	135.2 (82.3)	0.000	55.2 (52.7)	87.6 (69.7)	0.341
Lipids and Lipoproteins									
Total cholesterol, mg/dL	198.0 (49.0)	191.5 (43.8)	0.106	193.0 (41.0)	204.0 (44.4)	0.863	178.0 (38.0)	172.5 (32.6)	0.146
Triglycerides, mg/dL	84.0 (57.0)	109.6 (55.5)	0.259	117.0 (111.0)	116.0 (62.0)	0.956	116.0 (83.0)	125.5 (84.0)	0.303
RLP-C, mg/dL	5.1 (4.7)	6.2 (6.1)	0.732	8.6 (11.7)	7.0 (9.0)	0.514	5.7 (6.8)	7.2 (9.0)	0.399
LDL-C, mg/dL	117.4 (40.0)	113.4 (33.1)	0.768	117.7 (42.4)	113.4 (36.4)	0.694	105.9 (38.2)	108.2 (32.4)	0.402
calculated LDL-C, mg/dL	117.2 (42.9)	112.5 (40.0)	0.364	110.4 (41.8)	115.6 (37.8)	0.501	96.9 (31.7)	94.1 (31.6)	0.090
sdLDL-C, mg/dL	27.2 (17.3)	27.5 (12.2)	0.958	34.7 (20.8)	31.7 (22.5)	0.221	30.7 (19.2)	32.3 (19.2)	0.186
sdLDL-C/LDL-C ratio	0.230 (0.086)	0.245 (0.061)	0.762	0.298 (0.141)	0.269 (0.126)	0.213	0.285 (0.126)	0.295 (0.150)	0.224
lbLDL-C, mg/dL	88.0 (28.8)	85.9 (22.9)	0.699	82.3 (31.7)	80.6 (23.4)	0.774	74.1 (27.7)	75.2 (26.2)	0.883
LDL-TG, mg/dL	20.6 (9.4)	25.0 (9.4)	0.008	25.2 (12.1)	25.7 (8.7)	0.749	20.7 (7.7)	21.4 (9.3)	0.121
Non HDL-C, mg/dL	134.3 (48.5)	131.9 (49.5)	0.678	138.0 (44.4)	145.4 (39.7)	0.733	122.3 (38.5)	120.6 (31.1)	0.310
HDL-C, mg/dL	59.9 (18.6)	54.4 (17.8)	0.003	53.5 (16.4)	50.7 (15.6)	0.158	52.8 (16.6)	51.3 (12.7)	0.165
HDL$_2$-C, mg/dL	35.1 (15.5)	30.6 (12.7)	0.005	29.6 (12.4)	28.4 (8.9)	0.165	29.9 (12.1)	28.8 (9.3)	0.050
HDL$_3$-C, mg/dL	25.1 (4.5)	24.2 (5.9)	0.036	24.0 (5.6)	23.3 (4.5)	0.345	22.9 (5.6)	22.7 (5.3)	0.896
ApoE-HDL, mg/dL	5.8 (2.2)	5.1 (2.2)	0.004	5.1 (2.2)	4.7 (2.4)	0.118	4.7 (2.0)	4.7 (1.8)	0.366

* Obesity criteria based on Taiwan definitions of < or ≥ 27 kg/m^2, and data are expressed as median (interquartile range). The prevalence of obesity was 6.8%, 22.5%, and 36.4% in the NGT, prediabetic, and diabetic groups, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.

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prediabetics and diabetics, there is substantial residual risk seen in these subjects on statin treatment[19].

In the present study, fasting triglycerides were significantly higher in male and female prediabetic and diabetic subjects as compared with controls in all subjects, as well as in those on and off lipid-lowering medications, except for male prediabetics and female diabetics on lipid-lowering therapy. RLP-C levels were highest in prediabetics, and in this group, lipid-lowering treatment abolished these differences in men, but not in women. It is known that RLP-C may be an especially important CVD risk factor in women, and it is possible that the addition of fibrates or omega-3 fatty acids on top of statin therapy may be very important to minimize CVD risk[46]. With regard to direct LDL-C, calculated LDL-C, and lbLDL-C differences between prediabetes and diabetics versus control subjects were relatively small. An important novel finding in this study was that calculated LDL-C, using the Friedewald formula, significantly underestimated direct LDL-C with the assay used by slightly more than 10%. We therefore recommend the use of direct LDL-C in this population because it is the primary target of lipid-lowering therapy.

It should also be noted that sdLDL has been shown to be the more atherogenic component of LDL. Prediabetic subjects were most likely to have increases in this parameter, as compared with control subjects. However, sdLDL-C differences were greater in female prediabetic and diabetic subjects than in men, and the use of statin therapy in these subjects did not abolish differences in women. These finding indicate that possibly, either more intensive statin therapy or additional treatments such as fibrates or omega-3 fatty acids may be necessary to treat elevated TG-rich lipoproteins and sdLDL-C in prediabetic and diabetic subjects to minimize residual CVD risk[47].

LDL-TG, a new CVD marker, was highest in the prediabetic subjects, and statin therapy did not minimize these differences. Since a recent study has shown that LDL-TG levels are higher in CHD than in controls, our findings may be one of the reasons why prediabetes is linked to atherosclerosis[32]. However, it was unexpected that LDL-TG levels were lower in this population in diabetic subjects than in normal subjects. We have observed a modest positive correlation between HOMA$_\beta$ and LDL-TG, and since diabetics have lower HOMA$_\beta$ values, this may account for this difference. Whether this finding is also true in other populations remains to be confirmed. It should be noted that insulin deficiency and decreased HOMA$_\beta$ appears to be more common among Asian diabetics than that observed in western Caucasian populations where obesity and insulin resistance may be more common[47, 48]. This may also explain why we see differences in LDL-TG values in this population between prediabetic and diabetic subjects.

In addition, direct LDL-C levels were also lower in diabetic subjects, however, sdLDL-C levels were higher or similar to controls, resulting in sdLDL-C/LDL-C ratios in patients with T2DM that were significantly higher than in any other group. A previous study in a Japanese population has assessed cholesterol and TG in twenty lipoprotein subfractions, and documented that smaller LDL particles carry less TG than larger LDL and VLDL particles[49]. From this viewpoint, it makes sense that LDL-TG levels are lower in diabetics than in controls, since the number of sdLDL particles increases in patients with diabetes. Our overall data indicate that attempts to normalize sdLDL-C and LDL-TG levels in prediabetic and diabetic subjects need to be made to normalize their CVD risk.

Diabetics in our population and female prediabetics had significantly lower levels of HDL-C and HDL subfractions than controls, placing them at increased CVD risk. We have observed significant correlations between HDL-C, HDL$_3$-C, HDL$_2$-C, and apoE-HDL-C, and noted significantly lower values in diabetic men and prediabetic and diabetic women as compared to controls. These differences persisted for all parameters in patients on lipid-lowering treatment, except for HDL$_2$-C. It is still uncertain whether apoE-rich HDL particles are athero-protective. Similarly, there is an ongoing debate as to whether serum HDL$_3$-C is cardioprotective. While serum glucose levels in prediabetes are not high enough to be diagnosed as diabetes, overall, their lipid values are similar to those in diabetics. Our findings on the pattern of lipid profiles support the concept that CVD risk in prediabetics may be as high as in those with diabetes.

The strength of this study is the relatively large number of participants in the 3 groups for both genders. Moreover, we examined subjects on and off statin therapy. The data trends were very similar in all groups. In addition, all subjects were on stable therapy for their lipid alterations as well as for diabetes if present for at least 6 months prior to the study. While absolute values of lipid parameters are known to be influenced by lipid medications, the trends and differences observed when normal, prediabetics, and diabetics were compared, was not greatly different. The participants with diabetes were also taking anti-diabetes medications, mostly metformin, but all subjects receiving insulin were excluded. Metformin and other glucose-lowering medication may affect lipid profiles, but do not cause rapid changes since their diabetic conditions were stable and their medications were not changed for at least 6 months. While we only studied a Tai-

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wanese population, another limitation of this study, these findings need to be replicated in other populations using these newer lipoprotein assays. It should be noted that our study was cross-sectional, and prospective treatment studies in diabetics or prediabetics need to be performed on order to further assess potential changes in the various lipoprotein fractions measured.

Conclusion

In summary, we compared novel lipoprotein parameters in normal, prediabetic and diabetic subjects. Prediabetic subjects were more likely to have elevated TG, RLP-C, sdLDL-C, and LDL-TG, while diabetic subjects were more likely to have decreases in HDL-C and HDL subfractions than normal subjects. These findings indicate that in this large Asian population, prediabetes is associated with greater increases in atherogenic lipoproteins, while diabetes is more likely to be associated with low levels of HDL and its subfractions. These findings suggest that insulin resistance, as seen in prediabetics, plays an important role in modulating changes TG-rich lipoproteins, while both insulin resistance and impaired insulin production, as seen in the diabetic state, may be more important in the regulation of HDL and its subfractions. In our view, both increases in atherogenic lipoproteins and decreases in HDL and its subfractions modulates CVD risk. Weight loss may be the best strategy to improve these abnormalities, and in the case of atherogenic lipoproteins, the combination of statins, fibrates, and omega-3 fatty acids. Moreover, our data indicate that calculated LDL-C significantly underestimated direct LDL-C in subjects with diabetes. In our view, direct LDL-C and sdLDL-C should be measured and optimized in both diabetic and prediabetic subjects to reduce CVD risk.

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Conflict of Interests

YI is an employee of Denka-Seiken Corporation, MA is supported by a research grant from Denka-Seiken Co., Tokyo, Japan. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The research was approved by the ethics committee of the School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan. (Reference number: M2000-2350).

Contributorship

HH and MA designed and conducted the study. HH, PH, and MHC recruited study subjects and collected data. HH, EK, and MA, analyzed the data. HH, MA, and EJS wrote the first version of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental Table 1. Effects of Obesity Status (Japanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Men*

Variables	NGT			PreDM			DM		
	BMI < 25 n = 162	BMI ≧25 n = 108	P	BMI < 25 n = 94	BMI ≧25 n = 99	P	BMI < 25 n = 206	BMI ≧25 n = 331	P
Age, year	56.1 (21.0)	54.0 (20.7)	0.334	61.5 (19.3)	59.6 (18.0)	0.457	63.8 (15.9)	60.4 (14.2)	0.000
BMI, kg/m^2	22.6 (2.6)	26.7 (3.1)	0.000	23.2 (2.4)	27.2 (3.1)	0.000	23.1 (2.1)	28.0 (3.7)	0.000
Systolic BP, mmHg	121.0 (17.0)	124.0 (16.0)	0.009	123.0 (20.0)	130.0 (23.8)	0.000	130.0 (11.0)	130.0 (14.0)	0.836
Diastolic BP, mmHg	71.0 (15.0)	77.0 (12.0)	0.002	74.0 (14.0)	80.0 (13.8)	0.002	70.0 (10.0)	70.0 (10.0)	0.375
Fasting Glucose, mg/dL	92.0 (8.0)	93.0 (7.0)	0.046	104.5 (8.0)	105.0 (9.0)	0.496	134.5 (42.8)	133.0 (36.5)	0.934
HbA1c, %	5.5 (0.4)	5.5 (0.4)	0.215	5.8 (0.4)	5.8 (0.5)	0.671	6.8 (1.2)	7.0 (1.3)	0.078
Insulin,	6.3 (4.9)	11.9 (8.9)	0.000	8.8 (4.3)	13.0 (10.5)	0.000	7.5 (6.0)	13.3 (11.0)	0.000
HOMA-IR	1.4 (1.1)	2.6 (2.1)	0.000	2.3 (1.4)	3.5 (3.0)	0.000	2.6 (2.1)	4.4 (4.1)	0.000
HOMA-β	82.9 (61.0)	150.2 (111.6)	0.000	76.3 (39.0)	110.8 (81.4)	0.000	40.5 (44.5)	69.1 (66.4)	0.000
Lipids and Lipoproteins									
Total cholesterol, mg/dL	193.0 (53.0)	190.5 (58.3)	0.828	189.5 (45.3)	190.0 (41.0)	0.255	171.0 (37.8)	171.0 (42.0)	0.968
Triglycerides, mg/dL	94.0 (54.5)	125.0 (90.3)	0.000	108.0 (76.0)	142.0 (94.5)	0.004	102.0 (75.8)	128.0 (94.5)	0.000
RLP-C, mg/dL	5.7 (6.0)	8.3 (11.9)	0.593	7.1 (8.5)	10.1 (10.6)	0.018	5.0 (6.3)	7.9 (10.0)	0.002
LDL-C, mg/dL	111.4 (43.2)	113.8 (51.5)	0.480	107.3 (42.7)	118.3 (47.4)	0.031	106.8 (32.0)	106.6 (33.4)	0.448
calculated LDL-C, mg/dL	118.6 (50.1)	109.9 (46.5)	0.691	113.6 (43.4)	111.5 (42.5)	0.526	94.3 (30.6)	94.1 (36.1)	0.910
sdLDL-C, mg/dL	28.3 (18.8)	33.5 (29.1)	0.001	29.6 (19.8)	39.5 (24.1)	0.000	29.2 (18.7)	35.4 (21.9)	0.000
sdLDL-C/LDL-C ratio	0.247 (0.104)	0.289 (0.144)	0.000	0.272 (0.136)	0.317 (0.170)	0.003	0.267 (0.111)	0.320 (0.172)	0.000
lbLDL-C, mg/dL	81.9 (35.5)	77.8 (34.1)	0.170	78.1 (28.6)	79.5 (37.1)	0.631	75.5 (25.4)	72.1 (28.0)	0.028
LDL-TG, mg/dL	20.8 (10.3)	24.2 (11.4)	0.000	21.8 (8.1)	25.4 (10.1)	0.000	18.3 (7.6)	20.1 (7.8)	0.012
Non HDL-C, mg/dL	140.9 (53.8)	139.7 (58.9)	0.268	139.0 (42.3)	139.0 (45.8)	0.108	119.5 (33.9)	125.1 (37.4)	0.052
HDL-C, mg/dL	53.0 (19.1)	47.1 (16.7)	0.000	49.9 (18.0)	50.1 (14.2)	0.320	50.1 (15.0)	44.6 (11.5)	0.000
HDL$_2$-C, mg/dL	29.1 (13.6)	24.4 (9.7)	0.000	26.8 (11.1)	27.1 (9.6)	0.475	27.4 (10.3)	24.0 (7.1)	0.000
HDL$_3$-C, mg/dL	23.3 (5.6)	22.3 (5.4)	0.172	22.8 (5.3)	22.5 (5.4)	0.190	21.1 (4.9)	20.3 (5.1)	0.012
ApoE-HDL, mg/dL	4.8 (2.3)	4.3 (2.2)	0.001	4.7 (2.2)	4.7 (1.9)	0.515	4.2 (1.8)	3.7 (1.5)	0.000

*Obesity criteria based on Japanese criteria of < or ≥25 kg/m^2, and all data are expressed as median (interquartile range). The prevalence of obesity was 40.0%, 51.3%, and 61.6% in the NGT, prediabetic, and diabetic groups, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.

Supplemental Table 2. Effects of Obesity Status (Japanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Women*

Variables	Normal			PreDM			Diabetic		
	BMI < 25 n = 291	BMI ≧25 n = 90	P	BMI < 25 n = 88	BMI ≧25 n = 50	P	BMI < 25 n = 214	BMI ≧25 n = 259	P
Age, year	50.5 (16.7)	53.9 (19.8)	0.009	58.1 (18.2)	66.7 (17.2)	0.077	64.5 (13.2)	62.8 (12.9)	0.014
BMI, kg/m^2	21.8 (2.9)	26.6 (2.2)	0.000	22.3 (2.6)	28.0 (3.8)	0.000	22.9 (2.6)	27.9 (3.9)	0.000
Systolic BP, mmHg	116.5 (20.0)	121.0 (13.0)	0.002	122.0 (20.0)	125.0 (16.0)	0.004	130.0 (14.0)	130.0 (15.0)	0.076
Diastolic BP, mmHg	68.0 (14.0)	73.0 (12.5)	0.000	70.0 (12.3)	72.0 (15.5)	0.260	70.0 (10.0)	70.0 (10.0)	0.728
Fasting Glucose, mg/dL	89.0 (8.0)	92.0 (8.0)	0.022	105.0 (11.3)	105.0 (10.8)	0.356	131.0 (39.5)	133.0 (41.0)	0.040
HbA1c, %	5.4 (0.5)	5.6 (0.4)	0.001	5.9 (0.6)	6.0 (0.6)	0.012	6.9 (1.1)	7.0 (1.3)	0.037
Insulin,	7.5 (5.5)	10.7 (5.6)	0.000	11.1 (7.4)	14.8 (10.3)	0.002	9.4 (8.1)	15.7 (11.5)	0.000
HOMA-IR	1.6 (1.3)	2.3 (1.2)	0.000	2.8 (2.2)	4.0 (2.8)	0.011	3.3 (2.7)	5.3 (4.9)	0.000
HOMA-β	108.0 (71.9)	138.5 (102.6)	0.000	87.0 (59.5)	122.4 (74.0)	0.000	52.8 (49.3)	81.7 (77.6)	0.111
Lipids and Lipoproteins									
Total cholesterol, mg/dL	198.0 (49.0)	194.0 (47.9)	0.645	192.5 (42.8)	196.5 (45.0)	0.659	177.5 (35.1)	174.0 (38.5)	0.613
Triglycerides, mg/dL	80.0 (56.0)	108.6 (73.0)	0.000	114.5 (115.8)	126.0 (73.8)	0.295	116.0 (83.0)	122.0 (82.5)	0.133
RLP-C, mg/dL	4.7 (4.2)	6.8 (6.4)	0.980	7.9 (11.5)	9.0 (9.3)	0.626	5.4 (6.4)	6.8 (8.8)	0.129
LDL-C, mg/dL	115.0 (40.1)	119.6 (39.4)	0.180	117.6 (41.3)	113.9 (40.8)	0.918	105.1 (39.9)	108.4 (31.7)	0.219
calculated LDL-C, mg/dL	116.8 (41.4)	114.6 (45.5)	0.899	108.6 (41.3)	115.2 (38.7)	0.381	97.5 (32.0)	94.4 (32.5)	0.335
sdLDL-C, mg/dL	26.4 (15.0)	31.6 (19.4)	0.008	33.6 (20.5)	34.5 (22.5)	0.952	31.4 (18.8)	31.5 (20.2)	0.092
sdLDL-C/LDL-C ratio	0.226 (0.080)	0.256 (0.097)	0.003	0.294 (0.132)	0.275 (0.115)	0.913	0.285 (0.116)	0.293 (0.147)	0.122
lbLDL-C, mg/dL	87.8 (27.9)	87.5 (27.8)	0.824	82.6 (32.1)	80.6 (25.8)	0.920	72.3 (27.7)	75.6 (26.7)	0.673
LDL-TG, mg/dL	20.1 (8.3)	25.1 (9.1)	0.000	23.4 (11.1)	26.2 (8.8)	0.139	20.4 (7.6)	21.4 (8.6)	0.212
Non-HDL-C, mg/dL	131.3 (49.3)	137.3 (46.3)	0.241	135.8 (44.5)	145.2 (38.9)	0.217	121.6 (39.5)	122.0 (34.2)	0.988
HDL-C, mg/dL	60.8 (19.3)	55.6 (14.6)	0.000	53.8 (17.0)	51.1 (12.8)	0.030	53.0 (16.2)	51.8 (13.5)	0.157
HDL$_2$-C, mg/dL	36.0 (16.2)	30.8 (12.1)	0.000	30.4 (12.7)	28.1 (9.2)	0.014	30.1 (12.4)	28.9 (9.7)	0.050
HDL$_3$-C, mg/dL	25.2 (4.6)	24.9 (4.3)	0.037	24.0 (5.4)	23.3 (5.2)	0.493	23.0 (5.7)	22.6 (5.5)	0.957
ApoE-HDL, mg/dL	5.9 (2.4)	5.3 (1.8)	0.000	5.3 (2.1)	4.8 (1.9)	0.029	4.7 (2.0)	4.7 (1.8)	0.479

*Obesity criteria based on Japanese criteria of < or ≥25.0 kg/m^2, and all data are expressed as median (interquartile range). The prevalence of obesity was 26.4%, 36.2%, and 54.8% in the NGT, prediabetic, and diabetic subjects, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.

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Supplemental Table 3. Comparison of variables between normal participants with or without using statin*

Variables	Male Participants		*p*	Female Participants		*p*
	Statin − (*n* = 207)	Statin + (*n* = 62)		Statin − (*n* = 324)	Statin + (*n* = 60)	
Age, year	52.2 (18.3)	66.0 (16.2)	0.000	49.3 (12.9)	69.5 (13.0)	0.000
BMI, kg/m^2	23.9 (4.1)	24.7 (3.4)	0.044	22.5 (4.0)	24.0 (4.1)	0.001
Obesity Prevalence	36 (17.4%)**	14 (22.6%)**	0.009	25 (7.7%)**	10 (16.7%)**	0.003
Systolic BP, mmHg	122.0 (15.8)	130.0 (15.3)	0.097	117.0 (19.0)	129.5 (18.3)	0.000
Diastolic BP, mmHg	74.0 (13.0)	75.0 (10.8)	0.348	68.0 (14.0)	76.0 (10.5)	0.020
Fasting Glucose, mg/dL	92.0 (7.5)	94.0 (7.0)	0.182	89.5 (8.0)	92.0 (8.5)	0.000
HbA1c, %	5.5 (0.4)	5.6 (0.3)	0.584	5.4 (0.4)	5.6 (0.5)	0.000
Insulin,	7.9 (7.4)	8.5 (6.8)	0.494	7.9 (5.6)	10.1 (7.6)	0.004
HOMA-IR	1.8 (1.6)	1.9 (1.5)	0.578	1.8 (1.3)	2.3 (1.7)	0.001
HOMA-β	99.5 (96.2)	104.0 (68.5)	0.271	110.7 (76.0)	128.9 (85.5)	0.483
Lipids and Lipoproteins						
Total cholesterol, mg/dL	196.1 (50.5)	175.5 (57.2)	0.056	198.0 (47.3)	193.8 (56.0)	0.767
Triglycerides, mg/dL	103.0 (79.5)	100.5 (47.3)	0.260	81.0 (57.5)	107.6 (68.3)	0.000
RLP-C, mg/dL	6.3 (8.2)	5.7 (5.6)	0.309	4.8 (4.2)	7.4 (5.8)	0.842
LDL-C, mg/dL	116.7 (44.8)	102.1 (46.0)	0.194	117.7 (39.2)	112.5 (40.6)	0.285
calculated LDL-C, mg/dL	119.2 (44.3)	100.6 (51.9)	0.078	117.3 (40.7)	111.2 (52.1)	0.342
sdLDL-C, mg/dL	30.7 (22.9)	27.5 (15.0)	0.216	26.5 (16.8)	30.0 (17.2)	0.218
sdLDL-C/LDL-C ratio	0.256 (0.118)	0.265 (0.070)	0.460	0.226 (0.081)	0.278 (0.091)	0.000
lbLDL-C, mg/dL	84.9 (33.0)	76.0 (32.7)	0.324	89.8 (27.4)	81.7 (31.4)	0.019
LDL-TG, mg/dL	22.1 (11.3)	22.0 (8.2)	0.419	20.1 (9.9)	23.8 (6.1)	0.001
Non HDL-C, mg/dL	142.9 (52.2)	122.9 (51.7)	0.062	133.4 (48.1)	135.9 (53.9)	0.696
HDL-C, mg/dL	51.6 (18.1)	49.9 (16.0)	0.729	59.9 (18.8)	58.2 (15.4)	0.088
HDL_2-C, mg/dL	27.6 (13.0)	26.4 (12.9)	0.961	34.7 (16.1)	32.1 (11.1)	0.074
HDL_3-C, mg/dL	23.0 (5.8)	22.8 (4.2)	0.279	25.1 (4.7)	24.9 (3.9)	0.534
ApoE-HDL, mg/dL	4.6 (2.1)	4.5 (2.5)	0.962	5.7 (2.3)	5.8 (2.0)	0.354

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

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Supplemental Table 4. Comparison of variables between prediabetic participants with or without using statin*

Variables	Male Participants		*p*	Female Participants		*p*
	Statin − (n = 117)	Statin + (n = 79)		Statin − (n = 90)	Statin + (n = 52)	
Age, year	54.5 (18.5)	66.0 (12.7)	0.000	54.7 (19.2)	68.0 (12.8)	0.000
BMI, kg/m^2	25.3 (4.0)	25.0 (4.1)	0.067	24.1 (5.2)	23.5 (4.5)	0.079
Obesity Prevalence	36 (30.8%)**	16 (20.3%)**	0.888	23 (25.5%)**	8 (15.4%)**	0.371
Systolic BP, mmHg	130.0 (22.0)	127.0 (12.0)	0.309	120.0 (17.0)	130.0 (10.0)	0.041
Diastolic BP, mmHg	77.0 (17.0)	75.0 (11.0)	0.170	70.5 (11.8)	77.0 (12.0)	0.136
Fasting Glucose, mg/dL	105.0 (10.0)	106.0 (8.5)	0.563	105.0 (11.0)	104.5 (10.3)	0.158
HbA1c, %	5.8 (0.5)	5.9 (0.4)	0.807	5.8 (0.7)	5.9 (0.4)	0.544
Insulin,	10.6 (8.9)	11.2 (8.0)	0.319	11.9 (8.2)	13.4 (10.2)	0.566
HOMA-IR	2.7 (2.3)	3.0 (2.1)	0.449	3.2 (2.2)	3.4 (2.6)	0.899
HOMA-β	85.1 (63.5)	90.4 (51.9)	0.254	95.7 (64.5)	116.4 (75.1)	0.065
Lipids and Lipoproteins						
Total cholesterol, mg/dL	192.0 (32.0)	184.0 (56.0)	0.306	194.5 (38.5)	193.5 (54.5)	0.234
Triglycerides, mg/dL	133.0 (99.0)	111.0 (69.0)	0.119	106.5 (82.8)	131.5 (106.3)	0.002
RLP-C, mg/dL	10.1 (11.6)	7.4 (8.3)	0.029	7.0 (8.4)	9.5 (14.6)	0.012
LDL-C, mg/dL	115.5 (40.9)	106.7 (48.8)	0.579	118.1 (39.5)	110.0 (49.0)	0.124
calculated LDL-C, mg/dL	114.1 (38.0)	106.9 (47.7)	0.912	113.5 (36.2)	106.3 (55.2)	0.055
sdLDL-C, mg/dL	34.9 (26.1)	33.4 (22.4)	0.369	32.5 (22.5)	35.8 (21.4)	0.271
sdLDL-C/LDL-C ratio	0.310 (0.164)	0.288 (0.121)	0.356	0.272 (0.103)	0.330 (0.136)	0.002
lbLDL-C, mg/dL	79.7 (32.5)	73.8 (31.0)	0.902	84.4 (22.7)	72.2 (29.5)	0.004
LDL-TG, mg/dL	23.4 (10.9)	22.9 (8.8)	0.259	23.3 (10.6)	26.9 (10.1)	0.168
Non HDL-C, mg/dL	141.6 (33.2)	131.1 (50.3)	0.320	139.7 (38.8)	138.5 (54.9)	0.614
HDL-C, mg/dL	51.4 (18.0)	49.4 (13.8)	0.846	53.6 (16.7)	51.0 (12.6)	0.054
HDL_2-C, mg/dL	26.3 (12.4)	27.1 (7.9)	0.851	29.8 (13.7)	26.1 (9.1)	0.059
HDL_3-C, mg/dL	22.9 (5.5)	22.5 (5.3)	0.888	23.9 (5.4)	22.8 (4.9)	0.205
ApoE-HDL, mg/dL	4.8 (2.1)	4.6 (1.9)	0.919	5.2 (2.3)	4.9 (1.4)	0.259

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

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Supplemental Table 5. Comparison of variables between diabetic participants with or without using statin*

Variables	Male Participants		*p*	Female Participants		*p*
	Statin − (*n* = 281)	Statin + (*n* = 206)		Statin − (*n* = 208)	Statin + (*n* = 227)	
Age, year	61.9 (13.4)	62.4 (15.2)	0.521	63.6 (11.9)	64.3 (13.1)	0.286
BMI, kg/m^2	25.4 (4.7)	26.6 (4.9)	0.007	24.8 (4.8)	26.2 (5.4)	0.001
Obesity Prevalence	94 (33.5%)**	88 (42.7%)**	0.001	57 (27.4%)**	94 (41.4%)**	0.058
Systolic BP, mmHg	130.0 (14.0)	130.0 (10.0)	0.945	130.0 (19.5)	130.0 (10.0)	0.352
Diastolic BP, mmHg	76.0 (10.0)	70.0 (10.0)	0.419	70.0 (10.0)	70.0 (10.0)	0.257
Fasting Glucose, mg/dL	134.0 (35.0)	132.0 (39.8)	0.311	132.0 (39.5)	131.0 (42.0)	0.618
HbA1c, %	6.9 (1.1)	6.8 (1.4)	0.657	7.0 (1.2)	6.9 (1.3)	0.189
Insulin,	10.5 (10.7)	10.4 (7.9)	0.495	12.0 (9.4)	13.7 (10.5)	0.644
HOMA-IR	3.3 (3.7)	3.5 (3.0)	0.611	4.0 (3.6)	4.6 (3.9)	0.757
HOMA-β	55.2 (61.7)	60.0 (56.7)	0.522	60.9 (60.0)	69.2 (72.7)	0.155
Lipids and Lipoproteins						
Total cholesterol, mg/dL	171.0 (33.0)	168.0 (50.8)	0.214	178.0 (31.1)	172.0 (41.0)	0.971
Triglycerides, mg/dL	116.0 (91.0)	118.0 (88.3)	0.579	118.0 (75.0)	120.0 (78.0)	0.126
RLP-C, mg/dL	5.6 (8.0)	7.3 (9.4)	0.133	5.3 (6.1)	6.8 (8.7)	0.073
LDL-C, mg/dL	107.2 (30.1)	104.7 (40.9)	0.087	108.4 (29.7)	104.1 (39.6)	0.655
calculated LDL-C, mg/dL	94.1 (30.9)	92.7 (40.5)	0.141	101.0 (27.1)	91.3 (34.7)	0.099
sdLDL-C, mg/dL	31.8 (18.8)	33.2 (21.0)	0.056	29.4 (19.9)	32.8 (16.9)	0.039
sdLDL-C/LDL-C ratio	0.288 (0.139)	0.304 (0.140)	0.298	0.272 (0.124)	0.301 (0.131)	0.011
lbLDL-C, mg/dL	74.6 (25.2)	72.4 (26.8)	0.394	76.4 (24.1)	71.7 (27.8)	0.304
LDL-TG, mg/dL	18.1 (6.6)	20.0 (8.1)	0.003	19.3 (7.9)	21.7 (8.6)	0.000
Non HDL-C, mg/dL	122.8 (30.9)	119.5 (44.6)	0.257	124.4 (33.5)	117.3 (36.8)	0.454
HDL-C, mg/dL	46.0 (13.6)	46.8 (14.1)	0.587	50.3 (17.2)	54.0 (13.9)	0.034
HDL_2-C, mg/dL	25.2 (8.3)	25.4 (8.4)	0.736	28.4 (11.8)	30.3 (10.2)	0.144
HDL_3-C, mg/dL	20.5 (5.1)	20.9 (5.3)	0.409	22.2 (5.2)	23.4 (5.3)	0.002
ApoE-HDL, mg/dL	3.7 (1.5)	4.1 (1.8)	0.039	4.4 (2.0)	5.0 (1.8)	0.000

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m^2).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

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Supplemental Table 6. Correlations in all subjects***

	TG	RLP-C	LDL-C	Calculated LDL-C	sdLDL-C	sdLDL-C/ LDL-C	lbLDL-C	LDL-TG	HDL-C	HDL_2-C	HDL_3-C	ApoE-HDL
Age	−0.013	−0.01	−0.143**	−0.142**	−0.088**	−0.008	−0.131**	−0.024	−0.105**	−0.052*	−0.196**	−0.135**
BMI	0.205**	0.089**	0.026	−0.084**	0.174**	0.23**	−0.087**	0.138**	−0.274**	−0.288**	−0.153**	−0.254**
Systolic BP	0.152**	0.089**	0.014	−0.009	0.154**	0.219**	−0.088**	0.165**	−0.153**	−0.174**	−0.043	−0.136**
Diastolic BP	0.118**	0.051	0.052	0.033	0.157**	0.176**	−0.037	0.145**	−0.131**	−0.164**	0.001	−0.106**
Fasting Glucose	0.245**	0.097**	−0.055*	−0.194**	0.154**	0.26**	−0.183**	0.013	−0.129**	−0.117**	−0.115**	−0.158**
HbA1c	0.198**	0.071**	−0.052*	−0.186**	0.126**	0.21**	−0.16**	−0.007	−0.15**	−0.132**	−0.142**	−0.183**
Insulin	0.228**	0.115**	−0.009	−0.07**	0.115**	0.182**	−0.094**	0.134**	−0.178**	−0.167**	−0.146**	−0.168**
HOMA-IR	0.272**	0.138**	−0.024	−0.101**	0.116**	0.196**	−0.114**	0.109**	−0.152**	−0.141**	−0.128**	−0.149**
HOMA-β	0.104**	0.107**	0.036	0.024	0.063**	0.059**	0.004	0.173**	−0.11**	−0.099**	−0.099**	−0.09**
Total cholesterol	0.189**	0.197**	0.779**	0.907**	0.603**	0.167**	0.626**	0.461**	0.323**	0.214**	0.473**	0.438**
TG		0.618**	0.023	−0.084**	0.513**	0.737**	−0.333**	0.534**	−0.292**	−0.323**	−0.122**	−0.207**
RLP-C	0.618**		0.069**	0.027	0.377**	0.481**	−0.173**	0.332**	−0.102**	−0.121**	−0.025	−0.035
LDL-C	0.023	0.069**		0.779**	0.694**	0.106**	0.86**	0.476**	0.136**	0.064**	0.26**	0.241**
Calculated LDL-C	−0.084**	0.027	0.779**		0.447**	−0.065**	0.772**	0.381**	0.111**	0.026	0.276**	0.208**
sdLDL-C	0.513**	0.377**	0.694**	0.447**		0.76**	0.23**	0.677**	−0.083**	−0.178**	0.168**	0.05*
sdLDL-C/LDL-C	0.737**	0.481**	0.106**	−0.065**	0.76**		−0.396**	0.532**	−0.256**	−0.328**	−0.003	−0.156**
lbLDL-C	−0.333**	−0.173**	0.86**	0.772**	0.23**	−0.396**		0.164**	0.243**	0.213**	0.232**	0.291**
LDL-TG	0.534**	0.332**	0.476**	0.381**	0.677**	0.532**	0.164**		−0.202**	−0.257**	−0.003	−0.08**
non HDL-C	0.311**	0.247**	0.770**	0.920**	0.668**	0.275**	0.568**	0.564**	−0.044**	−0.144**	0.207**	0.089**
HDL-C	−0.292**	−0.102**	0.136**	0.111**	−0.083**	−0.256**	0.243**	−0.202**		0.961**	0.76**	0.971**
HDL_2-C	−0.323**	−0.121**	0.064**	0.026	−0.178**	−0.328**	0.213**	−0.257**	0.961**		0.551**	0.904**
HDL_3-C	−0.122**	−0.025	0.26**	0.276**	0.168**	−0.003	0.232**	−0.003	0.76**	0.551**		0.809**
ApoE-HDL	−0.207**	−0.035	0.241**	0.208**	0.05*	−0.156**	0.291**	−0.08**	0.971**	0.904**	0.809**	

*** Pearson correlations.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

* Significance between 0.05 and 0.01

** Significance less than 0.01

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Supplemental Table 7. Correlations in male subjects***

	TG	RLP-C	LDL-C	Calculated LDL-C	sdLDL-C	sdLDL-C/ LDL-C	lbLDL-C	LDL-TG	HDL-C	HDL_2-C	HDL_3-C	ApoE-HDL
Age	−0.159**	−0.063*	−0.129**	−0.099**	−0.205**	−0.172**	−0.024	−0.152**	−0.016	0.076*	−0.206**	−0.068*
BMI	0.225**	0.068*	0.05	−0.055	0.221**	0.271**	−0.092**	0.143**	−0.26**	−0.272**	−0.145**	−0.225**
Systolic BP	0.092*	0.052	0.043	0.017	0.147**	0.167**	−0.047	0.148**	−0.003	−0.035	0.068	0.019
Diastolic BP	0.089*	−0.002	0.088	0.079	0.15**	0.128**	0.013	0.137**	−0.057	−0.104*	0.069	−0.017
Fasting Glucose	0.199**	0.064*	−0.074*	−0.193**	0.109**	0.221**	−0.176**	−0.047	−0.108**	−0.082**	−0.128**	−0.145**
HbA1c	0.114**	0.014	−0.035	−0.154**	0.074*	0.13**	−0.1**	−0.091**	−0.099**	−0.064*	−0.138**	−0.142**
Insulin	0.195**	0.08*	0.041	−0.059	0.142**	0.16**	−0.047	0.123**	−0.18**	−0.161**	−0.159**	−0.166**
HOMA-IR	0.203**	0.081**	0.009	−0.099**	0.131**	0.173**	−0.082**	0.08**	−0.176**	−0.151**	−0.169**	−0.175**
HOMA-β	0.104**	0.048	0.071*	0.04	0.091**	0.065*	0.03	0.161**	−0.13**	−0.125**	−0.096**	−0.098**
Total cholesterol	0.192**	0.217**	0.785**	0.905**	0.628**	0.201**	0.595**	0.503**	0.331**	0.204**	0.484**	0.459**
TG		0.564**	0.015	−0.12**	0.548**	0.771**	−0.373**	0.6**	−0.263**	−0.311**	−0.072*	−0.164**
RLP-C	0.564**		0.113**	0.059	0.408**	0.477**	−0.142**	0.377**	−0.067*	−0.093**	0.012	0.01
LDL-C	0.015	0.113**		0.78**	0.673**	0.084**	0.848**	0.461**	0.157**	0.084**	0.258**	0.269**
Calculated LDL-C	−0.12**	0.059	0.78**		0.438**	−0.077*	0.767**	0.427**	0.135**	0.043	0.285**	0.239**
sdLDL-C	0.548**	0.408**	0.673**	0.438**		0.767**	0.178**	0.681**	−0.021	−0.138**	0.234**	0.13**
sdLDL-C/LDL-C	0.771**	0.477**	0.084**	−0.077*	0.767**		−0.438**	0.545**	−0.181**	−0.28**	0.091**	−0.065*
lbLDL-C	−0.373**	−0.142**	0.848**	0.767**	0.178**	−0.438**		0.125**	0.224**	0.21**	0.175**	0.265**
LDL-TG	0.6**	0.377**	0.461**	0.427**	0.681**	0.545**	0.125**		−0.167**	−0.233**	0.028	−0.031
non HDL-C	0.296	0.253	0.777	0.917	0.672	0.276	0.551	0.592	−0.001	−0.118	0.246	0.146
HDL-C	−0.263**	−0.067*	0.157**	0.135**	−0.021	−0.181**	0.224**	−0.167**		0.951**	0.759**	0.968**
HDL_2-C	−0.311**	−0.093**	0.084**	0.043	−0.138**	−0.28**	0.21**	−0.233**	0.951**		0.521**	0.883**
HDL_3-C	−0.072*	0.012	0.258**	0.285**	0.234**	0.091**	0.175**	0.028	0.759**	0.521**		0.813**
ApoE-HDL	−0.164**	0.01	0.269**	0.239**	0.13**	−0.065*	0.265**	−0.031	0.968**	0.883**	0.813**	

*** Pearson correlations.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

* Significance between 0.05 and 0.01

** Significance less than 0.01

Supplemental Table 8. Correlations in female subjects***

	TG	RLP-C	LDL-C	Calculated LDL-C	sdLDL-C	sdLDL-C/ LDL-C	lbLDL-C	LDL-TG	HDL-C	HDL_2-C	HDL_3-C	ApoE-HDL
Age	0.138**	0.047	−0.156**	−0.184**	0.03	0.177**	−0.237**	0.104**	−0.181**	−0.154**	−0.186**	−0.194**
BMI	0.176**	0.105**	0.014	−0.103**	0.116**	0.165**	−0.062	0.148**	−0.236**	−0.254**	−0.108**	−0.224**
Systolic BP	0.173**	0.114**	−0.001	−0.026	0.136**	0.236**	−0.093*	0.176**	−0.197**	−0.209**	−0.083*	−0.185**
Diastolic BP	0.107*	0.087*	0.034	0.001	0.131**	0.171**	−0.041	0.147**	−0.098*	−0.125**	0.017	−0.082*
Fasting Glucose	0.288**	0.13**	−0.034	−0.193**	0.195**	0.302**	−0.184**	0.076*	−0.13**	−0.13**	−0.086**	−0.155**
HbA1c	0.289**	0.136**	−0.068*	−0.218**	0.181**	0.306**	−0.221**	0.085**	−0.193**	−0.188**	−0.138**	−0.221**
Insulin	0.267**	0.153**	−0.05	−0.082**	0.1**	0.221**	−0.14**	0.143**	−0.206**	−0.196**	−0.157**	−0.199**
HOMA-IR	0.341**	0.193**	−0.049	−0.105**	0.114**	0.239**	−0.148**	0.13**	−0.163**	−0.158**	−0.12**	−0.16**
HOMA-β	0.119**	0.162**	0.012	0.008	0.055	0.074*	−0.022	0.187**	−0.137**	−0.118**	−0.135**	−0.123**
Total cholesterol	0.204**	0.184**	0.775**	0.913**	0.598**	0.158**	0.654**	0.411**	0.287**	0.188**	0.441**	0.399**
TG		0.684**	0.037	−0.035	0.468**	0.69**	−0.277**	0.471**	−0.308**	−0.326**	−0.153**	−0.23**
RLP-C	0.684**		0.021	−0.018	0.336**	0.486**	−0.206**	0.285**	−0.129**	−0.141**	−0.054	−0.066*
LDL-C	0.037	0.021		0.779**	0.727**	0.144**	0.876**	0.49**	0.108**	0.034	0.26**	0.216**
Calculated LDL-C	−0.035	−0.018	0.779**		0.463**	−0.042	0.779**	0.334**	0.072*	−0.01	0.26**	0.171**
sdLDL-C	0.468**	0.336**	0.727**	0.463**		0.753**	0.306**	0.683**	−0.115**	−0.196**	0.133**	0.012
sdLDL-C/LDL-C	0.69**	0.486**	0.144**	−0.042	0.753**		−0.328**	0.541**	−0.299**	−0.349**	−0.064*	−0.203**
lbLDL-C	−0.277**	−0.206**	0.876**	0.779**	0.306**	−0.328**		0.2**	0.231**	0.184**	0.268**	0.29**
LDL-TG	0.471**	0.285**	0.49**	0.334**	0.683**	0.541**	0.2**		−0.277**	−0.323**	−0.06	−0.161**
non HDL-C	0.331	0.242	0.784	0.924	0.667	0.280	0.591	0.535	−0.089	−0.179	0.173	0.039
HDL-C	−0.308**	−0.129**	0.108**	0.072*	−0.115**	−0.299**	0.231**	−0.277**		0.965**	0.737**	0.97**
HDL_2-C	−0.326**	−0.141**	0.034	−0.01	−0.196**	−0.349**	0.184**	−0.323**	0.965**		0.532**	0.908**
HDL_3-C	−0.153**	−0.054	0.26**	0.26**	0.133**	−0.064*	0.268**	−0.06	0.737**	0.532**		0.786**
ApoE-HDL	−0.23**	−0.066*	0.216**	0.171**	0.012	−0.203**	0.29**	−0.161**	0.97**	0.908**	0.786**	

*** Pearson correlations.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

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