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Original Article

Cholesterol levels of Japanese dyslipidaemic patients with various comorbidities: BioBank Japan

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ABSTRACT

Background: Controlling serum cholesterol is critical to prevent cardiovascular disease in patients with dyslipidaemia. Guidelines emphasise the need to select treatment for dyslipidaemia based on specific patient profiles; however, there is little information about the serum cholesterol levels of patients in each profile in Japan. Therefore, we aimed to describe the serum cholesterol levels and prevalence of uncontrolled cases in Japanese patients with dyslipidaemia.

Methods: We included data for patients with dyslipidaemia between 2003 and 2007 from the BioBank Japan Project (66 hospitals). Then, we reported their serum cholesterol levels by age, body mass index, glycaemic control (glycated haemoglobin A1c), blood pressure, smoking, drinking, comorbidity and medication profiles.

Results: We included 22,189 male and 21,545 female patients. The mean serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and non-HDL-C levels in males were 117.4 mg/dL, 51.0 mg/dL, 187.6 mg/dL and 153.6 mg/dL, respectively; the corresponding levels in females were 129.5 mg/dL, 60.5 mg/dL, 144.9 mg/dL and 157.9 mg/dL, respectively. In both males and females, the LDL-C levels were the highest in the following profiles: age 19–44 years, body mass index 18.5–22 kg/m^2, glycated haemoglobin A1c <6.0%, never smoker, chronic respiratory disease as a comorbidity and no medication use.

Conclusions: These data provide details of serum cholesterol levels by risk-factor profile in patients with dyslipidaemia and could add evidence of treatment decisions.

Introduction

Controlling serum cholesterol is important for the prevention of arteriosclerotic cardiovascular disease (ASCVD) in patients with lifestyle-related diseases. A meta-analysis reports the protective effect of lowering serum low-density lipoprotein cholesterol (LDL-C) levels by statin therapy for preventing cardiovascular events in individuals with and without diabetes.[1] Data also indicate that

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intensively lowering LDL-C may reduce the risks of major coronary events, revascularisation and stroke in patients with hyperlipidaemia.[2] However, in Japan, evidence for antidyslipidaemic treatments is scarce because there are few cohorts with long-term follow-up data from the onset of dyslipidaemia.

The 2011 guidelines published by the European Society of Cardiology and the European Atherosclerosis Society recommend profiling individuals by risk factors. The recommendations for lipid profiling to assess cardiovascular risk include type 2 diabetes, established cardiovascular disease (CVD), hypertension, smoking, body mass index (BMI) $\geq$30 kg/m^2, family history of premature CVD, chronic inflammatory disease, chronic kidney disease (CKD), family history of familial dyslipidaemia and age (males >40 and females >50 years).[3] The recommended treatment targets are set on the levels of LDL-C, triglycerides (TG), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B. In the 2013 American guideline issued by the American College of Cardiology and American Heart Association, the focus for ASCVD risk is serum LDL-C $\geq$190 mg/dL (4.91 mmol/l), diabetes and age.[4] Despite their differences, both guidelines underscore the importance of controlling cholesterol levels by pharmaceutical interventions and lifestyle modifications based on individual risk profiles.

In Japan, using an analysis of the risk of fatal macrovascular disease in a representative population,[5] the 2012 guidelines for treating dyslipidaemia recommends that physicians stratify patients by history of coronary arterial disease (CAD), diabetes, CKD, non-cardiogenic cerebral infarction and peripheral arterial disease.[6] However, there is lack of data on the clinical picture of serum cholesterol levels in Japanese patients with dyslipidaemia according to disease profile. The aim of this study was to understand cholesterol control among Japanese patients with dyslipidaemia in a hospital setting.

Methods

Participants

The BioBank Japan Project collected medical follow-up data for 200,000 patients with 47 diseases for the fiscal years between 2003 and 2007.[7] The details of this project have been published elsewhere.[8–10] In this cross-sectional study, we included more than 40,000 Japanese patients with physician-diagnosed dyslipidaemia from 66 hospitals, and we collected data of serum samples together with information from patients' medical records. In addition, annual information on survival, mortality and causes of death were collected from patients' medical records, residence registry and Ministry of Internal Affairs and Communications of Japan, based on the Vital Statistics Act.[11] To focus on adult patients receiving treatment for dyslipidaemia, we included those aged $\geq$19 years who had primary or secondary dyslipidaemia. Secondary causes of dyslipidaemia here included hypothyroidism, nephrotic syndrome, diabetes, primary biliary cirrhosis, obstructive jaundice, Cushing syndrome, drug induced dyslipidaemia, uraemia, systemic lupus erythematosus, drinking and obesity, etc., according to Japanese guidelines.[6]

Measurements

Serum samples and medical data were collected at enrolment from medical records.[7] In accordance with the guidelines,[6] serum LDL-C levels were estimated indirectly using the Friedwald equation,[12] because this is considered more precise than direct measurement.[13] In addition, because serum samples were taken in fasting and non-fasting states, serum non-HDL-C levels were evaluated (total cholesterol levels − HDL-C levels).[6] We report serum cholesterol levels by patient age, BMI, serum glucose and glycated haemoglobin A1c (HbA1c) levels, blood pressure, smoking, drinking, comorbidity and medication profile. Age was stratified into 19–44 years, 45–64 years, 65–79 years and 80 years or older. BMI was calculated as weight in kilograms divided by the square of height in metres; patients were divided into the groups <18.5, 18.5–22, more than 22 to 25, more than 25 to less than 30 (overweight) and $\geq$30 (obesity). Serum HbA1c levels were measured using values according to the Japan Diabetes Society (JDS) and converted to those consistent with the National Glycohemoglobin Standardization Program (NGSP).[14,15] We stratified the serum HbA1c level as <6.0% (42 mmol/mol), 6.0% to less than 6.5% (48 mmol/mol), 6.5% to less than 7.0% (53 mmol/mol), 7.0% to less than 8.0% (64 mmol/mol), 8.0% to less than 9.0% (75 mmol/mol) and $\geq$9.0%. Classification of blood pressure levels was according to The Japanese Society of Hypertension.[16] For comorbidities, a history of CAD included myocardial infarction and stable or unstable angina pectoris. In this study, CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at registration, even though the guideline for clinical practice requires continuation of this low level for 3 months or more.[17] History of chronic respiratory disease included asthma, chronic obstructive pulmonary disease, interstitial pneumonia, pulmonary fibrosis and pneumoconiosis. History of cancer included cancer of any organ or tissue. To analyse patients in each profile, we used data with all serum cholesterol levels.

Statistical analysis

We report the arithmetic means [standard deviations (SDs)] for age, BMI, LDL-C, HDL-C, TG, non-HDL-C, glycaemic control and blood pressure in patients with dyslipidaemia of BioBank Japan Project according to sex. For smoking and drinking habits, comorbidities and pharmaceutical interventions, we report the distributions. Next, we compared the means (SDs) of serum cholesterol levels by the profiles of age, BMI, serum glucose level, blood pressure, smoking and drinking habits, comorbidities and medication. Medication profiles composed of statin monotherapy, combination therapies of statin and another antihyperlipidaemic agent and no medication. Along with the means, we also compared the percentages of patients who had fulfilled the criteria for screening patients with dyslipidaemia at a high risk of ASCVD[6] to assess proportion of patients with uncontrolled dyslipidaemia in each profile. Because the data included serum LDL-C levels in non-fasting states, dyslipidaemia in the criteria for screening was judged as non-HDL-C $\geq$170 mg/dL, HDL-C <40 mg/dL or TG $\geq$150 mg/dL.[6] Comparisons of mean cholesterol levels and percentages of patients with uncontrolled dyslipidaemia by the profiles were based on the patients with full data of LDL-C, HDL-C, TG and total cholesterol levels. All statistical analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA).

Ethical considerations

The ethics committees of the Institute of Medical Science, The University of Tokyo, RIKEN Center for Integrative Medical Sciences and 12 cooperating medical institutions, approved the study protocol in accordance with the guidelines and regulations of the Declaration of Helsinki. The Japanese guidelines permit the use of data from medical examinations and information without consent if data are anonymous. Hence, informed consent was not required for the present investigation.

Results

Table 1 presents the characteristics and distributions of the 22,189 male and 21,545 female patients included with a diagnosis

Table 1
Characteristics of patients with a diagnosis of dyslipidaemia in the Biobank Japan data. Mean (standard deviation) or number (proportion).

Characteristics	Males	Females
No. (%)	22,189 (50.7)	21,545 (49.3)
Age, years	62.1 (11.9)	66.3 (10.8)
Body mass index, kg/m^2	24.8 (3.5)	24.1 (3.9)
LDL-C, mg/dL and mmol/L	117.4 (41.4) and 3.03 (1.07)	129.5 (35.8) and 3.35 (0.92)
HDL-C, mg/dL and mmol/L	51.0 (14.8) and 1.32 (0.38)	60.5 (16.7) and 1.56 (0.43)
TG, mg/dL and mmol/L	187.6 (150.8) and 2.12 (1.70)	144.9 (95.8) and 1.64 (1.08)
Non-HDL-C, mg/dL and mmol/L	153.6 (43.7) and 3.97 (1.13)	157.9 (37.9) and 4.08 (0.98)
HbA1c, % and mmol/mol	6.44 (1.21) and 46.9 (13.2)	6.40 (1.44) and 46.4 (15.7)
Systolic blood pressure, mm Hg	132.2 (16.0)	132.3 (16.8)
Diastolic blood pressure, mm Hg	78.1 (10.6)	76.2 (10.7)
Smoking, never/ex-/current, no.	6683/9521/5985	17,930/1750/1865
Current drinker, no. (%)	10,956 (49.4)	3340 (15.5)
Comorbidity, no. (%)		
Coronary arterial disease	7881 (35.5)	3333 (15.5)
Diabetes mellitus	7569 (34.1)	5346 (24.8)
Chronic kidney disease	7.778 (35.1)	7081 (32.9)
Cerebral infarction	2982 (13.4)	2395 (11.1)
Peripheral arterial disease (arteriosclerosis obliterans)	686 (3.1)	258 (1.2)
Cancer	1465 (76.6)	1709 (7.9)
Chronic respiratory disease	1086 (4.9)	1268 (5.9)
Medication		
Statin	10,086 (45.5)	10,907 (50.6)
Fibrate	1436 (6.5)	651 (3.0)
Polyunsaturated fatty acid	556 (2.5)	392 (1.8)
Nicotinic acid	342 (1.5)	551 (2.6)
Probucol	226 (1.0)	194 (0.9)
Bile acid sequestrants (resins)	150 (0.7)	219 (1.0)
Plant sterol (phytosterol)	10 (0.1)	27 (0.1)
Ezetimibe	2 (0.0)	0
Others	28 (0.1)	27 (0.1)
Lifestyle modification without medication	10,364 (46.7)	9469 (44.0)

HbA1c, glycated haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

of dyslipidaemia. The means for age and BMI among the male patients were 62.1 (SD: 11.9) years and 24.8 (SD: 3.5) kg/m^2, respectively, while the corresponding means for female patients were 66.3 (SD: 10.8) years and 24.1 (SD: 3.9) kg/m^2, respectively. The mean serum LDL-C, HDL-C, TG and non-HDL-C levels in male patients were 117.4 (SD: 41.4) mg/dL, 51.0 (SD: 14.8) mg/dL, 187.6 (SD: 150.8) mg/dL and 153.6 (SD: 43.7) mg/dL, respectively. In addition, being an ex-smoker was the most common smoking history (Table 2). The mean serum LDL-C, HDL-C, TG and non-HDL-C levels in the female patients were 129.5 (SD: 35.8) mg/dL, 60.5 (SD: 16.7) mg/dL, 144.9 (SD: 95.8) mg/dL and 157.9 (SD: 37.9) mg/dL, respectively. In females, being a never-smoker was the most common smoking history (Table 3). CAD in males and CKD in females were the most common comorbidity, and statin monotherapy was the most common pharmaceutical intervention.

Tables 2 and 3 also show the mean serum cholesterol levels and percentages of uncontrolled dyslipidaemia in male and female patients by age, BMI, glycaemic control, blood pressure, smoking habit, drinking habit, comorbidity and medication profile. In both males and females, mean LDL-C was highest for the following profiles: age 19–44 years, BMI 18.5–22 kg/m^2, glycated haemoglobin A1c levels <6.0% (<42 mmol/mol), never smoker, chronic respiratory disease as a comorbidity and no medication use. In blood pressure profiles, LDL-C was the highest for systolic levels ≥180 mm Hg or diastolic levels ≥100 mm Hg in both sexes. In both sexes, there was also a slight difference in LDL-C and non-HDL-C levels between the non-drinkers and current drinkers, with HDL-C levels higher in current drinkers than in non-drinkers.

In males, uncontrolled dyslipidaemia was most prevalent in those with the following characteristics: age 19–44 years, BMI ≥30 kg/m^2, HbA1c levels ≥9.0%, systolic blood pressure <180 mm Hg and diastolic blood pressure <110 mm Hg, current smoker, non-drinker, and with chronic kidney disease as a comorbidity as well as in those with no medication use. In females, uncontrolled dyslipidaemia was most prevalent for those with the following characteristics: age 19–44 years, BMI ≥30 kg/m^2, HbA1c levels 8.0%–9.0%, systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg, current smoker, non-drinker, and with peripheral arterial disease as a comorbidity as well as in those with no medication use.

Discussion

Data have revealed detailed serum cholesterol levels (LDL-C, HDL-C, TG and non-HDL-C) in male and female patients with a diagnosis of dyslipidaemia. On average, patients were in their sixties and had a high-normal BMI (22–25 kg/m^2).

Interpretations in the context of previous studies

We should interpret the data for serum LDL-C levels carefully. Although serum LDL-C is considered the best management target for CVD prevention, the Japanese guidelines recommend physicians to use the non-HDL-C level as a secondary management target, particularly when the serum samples are obtained from non-fasting blood or when the serum TG level is ≥400 mg/dL.[6] Indeed, epidemiologic studies suggest that non-HDL-C has the potential to predict CVD more accurately than LDL-C.[18,19] The guidelines also provide physicians two options of treatment for patients with dyslipidaemia: lifestyle modifications and pharmacological interventions.[6] We consider that physicians in clinical practice could refer to the results of mean cholesterol levels of patients receiving the two treatments and the proportions of the patients at a risk of ASCVD in uncontrolled dyslipidaemia. Additionally, the patients were registered at hospitals and not at primary care clinics, so they were more likely to have comorbidities and unhealthy habits (smoking or drinking).

Table 2
Serum cholesterol levels of male patients with dyslipidaemia according to characteristics in the BioBank Japan data. Means (standard deviations) in mg/dL and mmol/L.

Characteristic	Males					
	No.	LDL-C	HDL-C	Triglyceride	Non-HDL	Percent fulfilling the screening criteria for dyslipidaemia
Age						
19–44	1265	125 (45) and 3.24 (1.17)	49 (13) and 1.27 (0.34)	236 (186) and 2.66 (2.10)	172 (46) and 4.46 (1.20)	81.0%
45–64	6427	118 (46) and 3.05 (1.20)	51 (14) and 1.32 (0.37)	191 (133) and 2.15 (1.50)	156 (47) and 4.04 (1.23)	68.6%
65–79	5560	115 (35) and 2.98 (0.90)	51 (14) and 1.32 (0.37)	160 (93) and 1.81 (1.06)	147 (36) and 3.81 (0.93)	59.2%
80+	648	114 (32) and 2.96 (0.63)	53 (15) and 1.36 (0.38)	144 (79) and 1.62 (0.89)	143 (34) and 3.70 (0.88)	53.4%
Body mass index						
−18.5	998	116 (37) and 2.99 (0.96)	53 (16) and 1.37 (0.42)	175 (138) and 1.98 (1.56)	151 (41) and 3.90 (1.05)	61.9%
18.5–22	2149	119 (49) and 3.07 (1.27)	55 (16) and 1.42 (0.42)	151 (104) and 1.70 (1.18)	149 (51) and 3.85 (1.31)	53.6%
22–25	5127	117 (43) and 3.03 (1.11)	52 (14) and 1.33 (0.37)	172 (116) and 1.95 (1.31)	152 (45) and 3.93 (1.15)	62.5%
25–30	4668	118 (37) and 3.04 (0.96)	49 (13) and 1.26 (0.33)	195 (127) and 2.20 (1.43)	157 (39) and 4.05 (1.00)	71.3%
30+	958	116 (38) and 2.99 (0.98)	46 (11) and 1.19 (0.28)	228 (165) and 2.57 (1.86)	161 (40) and 4.17 (1.03)	80.1%
Serum glucose, HbA1c						
<6.0% (42 mmol/mol)	8991	119 (44) and 3.08 (1.14)	52 (14) and 1.34 (0.37)	178 (122) and 2.01 (1.37)	155 (45) and 4.00 (1.17)	64.9%
6.0%–6.5% (48 mmol/mol)	1765	114 (36) and 2.94 (0.92)	50 (15) and 1.29 (0.38)	179 (120) and 2.02 (1.35)	149 (38) and 3.86 (0.99)	64.4%
6.5%–7.0% (53 mmol/mol)	1073	114 (36) and 2.94 (0.94)	50 (14) and 1.30 (0.37)	180 (133) and 2.03 (1.50)	150 (40) and 3.87 (1.04)	64.6%
7.0%–8.0% (64 mmol/mol)	1169	115 (35) and 2.97 (0.91)	48 (13) and 1.25 (0.32)	186 (130) and 2.10 (1.47)	152 (38) and 3.94 (0.98)	66.2%
8.0%–9.0% (75 mmol/mol)	510	115 (37) and 2.99 (0.97)	48 (13) and 1.23 (0.34)	200 (147) and 2.26 (1.66)	156 (41) and 4.02 (1.07)	68.6%
≥9.0% (75 mmol/mol)	392	118 (39) and 3.05 (1.00)	47 (13) and 1.22 (0.33)	208 (156) and 2.35 (1.77)	160 (41) and 4.13 (1.06)	71.4%
Blood pressure						
SBP <120 mm Hg and DBP <80 mm Hg	3523	118 (39) and 3.05 (1.00)	50 (14) and 1.29 (0.37)	178 (128) and 2.01 (1.45)	154 (41) and 3.97 (1.07)	65.6%
SBP <130 mm Hg and DBP <85 mm Hg	2731	116 (35) and 3.00 (0.91)	51 (15) and 1.33 (0.38)	176 (120) and 1.98 (1.36)	151 (38) and 3.90 (0.99)	63.0%
SBP <140 mm Hg and DBP <90 mm Hg	4029	117 (50) and 3.04 (1.30)	51 (14) and 1.33 (0.37)	183 (128) and 2.07 (1.44)	154 (51) and 3.98 (1.33)	65.5%
SBP <160 mm Hg and DBP <100 mm Hg	3183	118 (37) and 3.04 (0.95)	51 (14) and 1.32 (0.36)	183 (120) and 2.06 (1.35)	154 (38) and 3.98 (0.98)	65.9%
SBP <180 mm Hg and DBP <110 mm Hg	391	118 (37) and 3.06 (0.95)	51 (14) and 1.33 (0.37)	198 (146) and 2.24 (1.65)	158 (39) and 4.08 (1.00)	70.6%
SBP ≥180 mm Hg or DBP ≥110 mm Hg	43	129 (55) and 3.35 (1.41)	53 (16) and 1.37 (0.41)	209 (135) and 2.36 (1.53)	171 (63) and 4.43 (1.62)	67.4%
Smoking						
Never smoker	3850	121 (44) and 3.12 (1.13)	52 (15) and 1.35 (0.38)	169 (113) and 1.90 (1.27)	154 (45) and 3.99 (1.17)	63.0%
Ex-smoker	6200	115 (36) and 2.98 (0.92)	51 (14) and 1.32 (0.37)	172 (113) and 1.94 (1.28)	150 (38) and 3.87 (0.98)	62.1%
Current smoker	3850	117 (47) and 3.03 (1.21)	49 (14) and 1.28 (0.36)	207 (150) and 2.34 (1.69)	158 (48) and 4.10 (1.25)	72.6%
Alcohol drinking						
Non-drinker	5653	119 (36) and 3.08 (0.94)	48 (12) and 1.23 (0.32)	172 (109) and 1.94 (1.23)	153 (39) and 3.97 (1.01)	66.3%
Current drinker	7693	116 (45) and 3.01 (1.17)	53 (15) and 1.38 (0.39)	188 (136) and 2.12 (1.53)	154 (46) and 3.98 (1.20)	65.0%
Comorbidity						
Coronary arterial disease	4931	109 (33) and 2.83 (0.86)	48 (13) and 1.27 (0.34)	162 (100) and 1.83 (1.13)	142 (36) and 3.67 (0.92)	59.6%
Diabetes mellitus	4832	115 (36) and 2.97 (0.93)	49 (14) and 1.27 (0.36)	184 (134) and 2.07 (1.51)	151 (40) and 3.92 (1.03)	64.7%
Chronic kidney disease	4027	116 (44) and 3.00 (1.13)	49 (14) and 1.27 (0.35)	178 (117) and 2.01 (1.33)	152 (46) and 3.92 (1.19)	65.7%
Cerebral infarction	1884	118 (50) and 3.05 (1.29)	51 (14) and 1.31 (0.36)	167 (99) and 1.89 (1.12)	152 (52) and 3.92 (1.34)	61.3%
Peripheral arterial disease	445	111 (34) and 2.88 (0.88)	47 (14) and 1.23 (0.37)	167 (98) and 1.89 (1.11)	145 (36) and 3.75 (0.94)	64.0%
Cancer	749	115 (35) and 2.98 (0.91)	52 (15) and 1.34 (0.40)	169 (109) and 1.91 (1.23)	149 (36) and 3.86 (0.94)	62.8%
Chronic respiratory disease	643	120 (36) and 3.11 (0.94)	52 (14) and 1.35 (0.40)	174 (118) and 1.97 (1.33)	155 (40) and 4.02 (1.04)	65.2%
Medication						
Statin monotherapy	6285	111 (40) and 2.88 (1.05)	52 (14) and 1.35 (0.37)	168 (114) and 1.90 (1.29)	145 (43) and 3.75 (1.12)	57.9%
Statin and nicotinic acid	115	108 (32) and 2.80 (0.83)	53 (14) and 1.37 (0.37)	172 (139) and 1.95 (1.57)	143 (40) and 3.69 (1.04)	56.5%
Statin and bile acid sequestrants (resins)	26	108 (36) and 2.80 (0.94)	54 (14) and 1.40 (0.36)	217 (191) and 2.44 (2.15)	152 (34) and 3.92 (0.88)	65.4%
Statin and fibrate	0	–	–	–	–	–
Statin and polyunsaturated fatty acid	0	–	–	–	–	–
Statin and probucol	0	–	–	–	–	–
Lifestyle modification without medication	5861	125 (42) and 3.22 (1.10)	50 (14) and 1.30 (0.37)	185 (123) and 2.08 (1.39)	161 (43) and 4.18 (1.11)	71.1%

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Because the aim of this study was to provide a comprehensive picture of Japanese patients with dyslipidaemia in a hospital setting, we included all patients regardless of comorbidity. Hence, the data from this study may only represent the features of patients with moderate-to-severe hyperlipidaemia (Tables 1–3), and may not be applicable to patients who have slightly higher serum cholesterol levels and need only lifestyle modification.

Implications for clinical practice

Interestingly, the healthiest profiles did not always reflect the best serum cholesterol levels (Tables 2 and 3). In both sexes, the youngest age group (age 19–44 years) had the highest mean LDL-C and TG levels, while the low-normal BMI group (18.5–22 kg/m^2) had the highest mean LDL-C level. The lowest

Table 3
Serum cholesterol levels of female patients with dyslipidaemia according to characteristics in the BioBank Japan data. Means (standard deviations) in mg/dL and mmol/L.

Characteristic	Females					
	No.	LDL-C	HDL-C	Triglyceride	Non-HDL	Percent fulfilling the screening criteria for dyslipidaemia
Age						
19–44	459	135 (40) and 3.50 (1.03)	58 (17) and 1.51 (0.44)	166 (144) and 1.88 (1.63)	169 (41) and 4.36 (1.06)	65.1%
45–64	5326	134 (38) and 3.45 (0.97)	62 (16) and 1.60 (0.42)	145 (92) and 1.64 (1.04)	163 (40) and 4.20 (1.02)	57.0%
65–79	6773	127 (34) and 3.28 (0.88)	60 (15) and 1.54 (0.40)	141 (77) and 1.59 (0.87)	155 (36) and 4.01 (0.92)	52.4%
80+	1193	123 (34) and 3.18 (0.88)	59 (16) and 1.53 (0.41)	133 (69) and 1.50 (0.78)	149 (36) and 3.86 (0.94)	46.7%
Body mass index						
−18.5	1451	130 (38) and 3.36 (0.99)	63 (18) and 1.64 (0.48)	136 (86) and 1.54 (0.97)	157 (40) and 4.07 (1.05)	50.7%
18.5–22	3274	130 (35) and 3.37 (0.91)	65 (17) and 1.68 (0.45)	124 (78) and 1.40 (0.88)	155 (37) and 4.01 (0.95)	46.6%
22–25	4314	130 (35) and 3.36 (0.91)	60 (15) and 1.55 (0.38)	140 (80) and 1.58 (0.91)	158 (37) and 4.08 (0.96)	53.8%
25–30	3783	128 (36) and 3.31 (0.93)	57 (14) and 1.48 (0.36)	157 (91) and 1.77 (1.03)	160 (38) and 4.13 (0.97)	59.9%
30+	929	129 (36) and 3.33 (0.92)	55 (14) and 1.41 (0.35)	169 (94) and 1.91 (1.06)	163 (39) and 4.20 (1.00)	63.3%
Serum glucose, HbA1c						
<6.0% (42 mmol/mol)	9841	131 (36) and 3.39 (0.92)	62 (16) and 1.60 (0.42)	138 (82) and 1.55 (0.92)	159 (38) and 4.10 (0.97)	53.0%
6.0%–6.5% (48 mmol/mol)	1519	126 (35) and 3.27 (0.91)	58 (15) and 1.51 (0.38)	147 (80) and 1.66 (0.91)	156 (37) and 4.03 (0.96)	55.2%
6.5%–7.0% (53 mmol/mol)	830	126 (36) and 3.25 (0.92)	57 (15) and 1.46 (0.40)	156 (94) and 1.76 (1.06)	157 (38) and 4.05 (0.98)	57.5%
7.0%–8.0% (64 mmol/mol)	837	123 (35) and 3.19 (0.89)	56 (15) and 1.46 (0.38)	152 (88) and 1.71 (0.99)	154 (37) and 3.97 (0.95)	54.4%
8.0%–9.0% (75 mmol/mol)	393	122 (36) and 3.16 (0.94)	55 (16) and 1.43 (0.40)	174 (123) and 1.97 (1.39)	157 (39) and 4.06 (1.00)	62.1%
≥9.0% (75 mmol/mol)	331	128 (39) and 3.31 (1.00)	55 (15) and 1.43 (0.40)	172 (115) and 1.94 (1.29)	162 (44) and 4.20 (1.15)	61.0%
Blood pressure						
SBP <120 mm Hg and DBP <80 mm Hg	3627	133 (37) and 3.44 (0.97)	61 (16) and 1.58 (0.42)	138 (85) and 1.56 (0.96)	161 (39) and 4.16 (1.02)	54.5%
SBP <130 mm Hg and DBP <85 mm Hg	2643	128 (35) and 3.31 (0.91)	61 (16) and 1.59 (0.42)	138 (85) and 1.56 (0.96)	156 (37) and 4.02 (0.96)	50.4%
SBP <140 mm Hg and DBP <90 mm Hg	3912	128 (36) and 3.31 (0.92)	60 (15) and 1.55 (0.40)	144 (88) and 1.62 (0.99)	157 (38) and 4.05 (0.97)	54.2%
SBP <160 mm Hg and DBP <100 mm Hg	3115	129 (34) and 3.33 (0.88)	60 (16) and 1.54 (0.41)	148 (82) and 1.67 (0.93)	158 (36) and 4.09 (0.93)	56.3%
SBP <180 mm Hg and DBP <110 mm Hg	398	127 (35) and 3.27 (0.91)	58 (17) and 1.50 (0.43)	152 (93) and 1.72 (1.05)	157 (36) and 4.06 (0.94)	54.3%
SBP ≥180 mm Hg or DBP ≥110 mm Hg	56	140 (48) and 3.61 (1.24)	57 (14) and 1.46 (0.36)	173 (98) and 1.95 (1.10)	174 (55) and 4.51 (1.42)	71.4%
Smoking						
Never smoker	11,433	130 (35) and 3.36 (0.91)	61 (16) and 1.57 (0.41)	139 (82) and 1.57 (0.92)	158 (37) and 4.08 (0.96)	53.0%
Ex-smoker	1108	125 (38) and 3.24 (0.99)	59 (16) and 1.53 (0.41)	150 (91) and 1.70 (1.03)	156 (40) and 4.02 (1.04)	55.7%
Current smoker	1210	130 (39) and 3.36 (1.00)	57 (16) and 1.49 (0.42)	168 (110) and 1.90 (1.24)	163 (41) and 4.22 (1.05)	62.5%
Alcohol drinking						
Non-drinker	10,745	129 (36) and 3.34 (0.92)	59 (15) and 1.53 (0.40)	143 (86) and 1.62 (0.97)	158 (38) and 4.08 (0.98)	54.4%
Current drinker	2620	131 (36) and 3.38 (0.94)	65 (17) and 1.67 (0.44)	138 (86) and 1.56 (0.97)	158 (37) and 4.09 (0.96)	51.8%
Comorbidity						
Coronary arterial disease	2031	120 (35) and 3.10 (0.90)	56 (15) and 1.46 (0.39)	143 (82) and 1.61 (0.93)	148 (37) and 3.84 (0.95)	49.8%
Diabetes mellitus	3437	125 (37) and 3.23 (0.95)	56 (15) and 1.45 (0.38)	155 (97) and 1.75 (1.09)	156 (40) and 4.03 (1.04)	55.9%
Chronic kidney disease	3773	127 (36) and 3.27 (0.94)	59 (16) and 1.50 (0.42)	149 (87) and 1.68 (0.99)	156 (39) and 4.04 (1.00)	55.3%
Cerebral infarction	1507	126 (35) and 3.27 (0.90)	58 (16) and 1.49 (0.40)	145 (83) and 1.63 (0.94)	155 (37) and 4.01 (0.97)	52.8%
Peripheral arterial disease	172	126 (36) and 3.26 (0.94)	54 (18) and 1.39 (0.45)	148 (74) and 1.67 (0.83)	156 (36) and 4.03 (0.94)	61.6%
Cancer	922	128 (35) and 3.30 (0.90)	61 (17) and 1.57 (0.43)	148 (86) and 1.67 (0.98)	157 (36) and 4.06 (0.93)	55.6%
Chronic respiratory disease	763	129 (38) and 3.33 (0.99)	61 (16) and 1.57 (0.43)	146 (99) and 1.65 (1.12)	158 (41) and 4.08 (1.06)	55.4%
Medication						
Statin monotherapy	6981	122 (35) and 3.17 (0.90)	61 (16) and 1.58 (0.40)	138 (78) and 1.56 (0.88)	150 (37) and 3.88 (0.97)	46.7%
Statin and nicotinic acid	231	119 (35) and 3.08 (0.91)	63 (19) and 1.63 (0.48)	143 (85) and 1.61 (0.96)	148 (36) and 3.82 (0.94)	44.6%
Statin and bile acid sequestrants (resins)	26	132 (41) and 3.43 (1.06)	60 (15) and 1.55 (0.38)	149 (76) and 1.69 (0.86)	162 (48) and 4.20 (1.24)	53.9%
Statin and fibrate	0	–	–	–	–	–
Statin and polyunsaturated fatty acid	0	–	–	–	–	–
Statin and probucol	0	–	–	–	–	–
Lifestyle modification without medication	5462	139 (35) and 3.60 (0.89)	60 (16) and 1.55 (0.42)	144 (85) and 1.63 (0.96)	168 (36) and 4.35 (0.92)	63.0%

DBP, diastolic blood pressure; HbA1c, glycated haemoglobin A1c; SBP, systolic blood pressure.

HbA1c level (<6.0%; 42 mmol/mol) was also associated with the highest mean LDL-C level; however, higher serum HbA1c levels were still associated with proportionally lower HDL-C and higher TG levels. In contrast, higher LDL-C, TG and non-HDL-C levels and lower HDL-C levels, tended not to be consistently associated with higher blood pressure. We should consider these phenomena in terms of ageing process, menopause, genetic predisposition for hypercholesterolaemia, insulin resistance and an increased likelihood of opting for medical therapy with increased age. Patients with a diagnosis of hyperlipidaemia in the youngest group were considered to have genetic factors that increased their likelihood of hyperlipidaemia. Insulin-resistant fat cells increase the release of free fatty acids,[20] and this increase promotes TG production and very low-density lipoprotein cholesterol (VLDL-C) secretion from the liver.[21] The increased TG and VLDL-C levels then result in decreased serum HDL-C levels.[22] Insulin resistance also makes both intracellular lipid uptake and weight gain difficult, which may increase the propensity for

patients to be underweight with concomitant poor serum cholesterol control. Having diabetes, with poor insulin secretion and action, can also disturb TG utilisation as an energy source. Evidence indicates that insulin resistance may independently worsen serum TG and HDL-C levels.[23] Despite these facts, when patients with diabetes are treated for other lifestyle-related diseases, serum cholesterol levels may actually improve in clinical practice.

In vivo research has revealed that smoking can lower serum HDL-C levels.[24,25] In our epidemiologic results, there were also slight but reduced serum HDL-C levels in current smokers followed by ex-smokers for both sexes (Tables 2 and 3). The observation that patients who were current drinkers had higher HDL-C levels than non-drinkers is also consistent with the literature on this topic.[26,27] However, we cannot provide a clear explanation for the variation in cholesterol levels by statin monotherapy or when used with another medicine. Given that physicians often prescribe non-statin antihyperlipidaemic medicines with statins when control of hyperlipidaemia is difficult,[6] the group treated with statin monotherapy possibly reflected patients with better response to treatment. Patients without medication also had the worst serum cholesterol levels, regardless of sex. That may be because patients without medication rejected their medicines or because at the time, there was lack of convincing evidence or guidelines for choosing statin therapy or other pharmaceutical interventions, which motivated physicians to select treatment by lifestyle modification.

The percentages of patients with uncontrolled dyslipidaemia (Table 2 for males and Table 3 for females) provide useful data that can help in clinical practice. The fact that the highest proportion of patients with uncontrolled dyslipidaemia was among those without medication emphasises the necessity of early pharmacological intervention for patients who were initially treated with lifestyle modification. The youngest patients with dyslipidaemia, registered in hospitals, may have had genetic predispositions of more severe forms of dyslipidaemia. Interestingly, patients with a BMI <18.5 kg/m^2 had the second lowest and not the lowest, proportion of uncontrolled dyslipidaemia. Previous Japanese data report that the lowest risk of hyperlipidaemia occurs among patients with BMIs of 20–24.9 kg/m^2, but that the hyperlipidaemic risk for underweight patients (BMI <18.5 kg/m^2) was not known.[28] Reportedly, a relatively large proportion of Japanese people with a BMI <25 kg/m^2 have excess visceral fat,[29] and normal BMI with fat accumulation is also known to increase serum total cholesterol levels and atherosclerotic risk factors.[30] In addition, the Japanese guidelines for controlling dyslipidaemia recommend comprehensive risk management of lifestyle-related diseases for the prevention of ASCVD.[6] Because our data indicate a high prevalence of uncontrolled dyslipidaemia among patients with uncontrolled diabetes, this patient group requires a more comprehensive risk management strategy in clinic and hospital settings. Moreover, cigarette smoking is an independent risk factor for all-cause and cardiovascular mortality,[31] and it has been shown that simple antismoking education for 3 min can increase the likelihood of successfully quitting smoking.[32] Because our data indicate a high prevalence of uncontrolled dyslipidaemia in current smokers, the Japanese government could do more to strengthen countermeasures against cardiovascular risk in smokers with a high prevalence of uncontrolled dyslipidaemia.

Limitations and strengths

Several limitations should be noted concerning this work. First, although the population size was very large, the data was relatively old. An important question for future studies is to determine serum cholesterol levels in a more current Japanese population. Second, because we invited patients from medium to large hospitals, the data may not reflect patients with mild dyslipidaemia who typically attend follow-up in smaller primary care clinics. Moreover, this limitation may have biased the serum cholesterol levels toward the higher end of the spectrum, making the data not applicable to patients with mild dyslipidaemia. Third, because LDL-C levels are best measured in the fasting state, the fact that some data were measured in the non-fasting state might attenuate the impact of the mean LDL-C levels.

Despite the limitations mentioned, there are several strengths of this work. First, the data are from a large Japanese population from numerous hospitals, and they provide detailed information on the serum cholesterol levels by risk profile in patients with dyslipidaemia. These data may help clinicians in the management of serum cholesterol by age, BMI, lifestyle-related disease, and smoking and drinking habits. Second, we were also able to describe the distribution of antihyperlipidaemic medicine use between 2003 and 2007. The data clarify that in Japan, numerous patients were treated with nicotinic acid and resins combined with statins at the time of this research. Because little is known about the effect of pharmaceutical interventions other than statins,[4] further analysis of other medicines for CVD prevention is necessary.

Conclusions

In this study, we have summarised the serum cholesterol levels among Japanese patients in a hospital setting by age, BMI, comorbidity, and smoking and drinking risk profiles. The mean cholesterol levels identified in the individual profiles should help physicians with the management of patients with dyslipidaemia in clinical practice.

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Author contributions

MK and ZY conceived the study. ZY, HY and MK designed the study. HY performed statistical analysis and wrote the manuscript. AN, TN, YK and MH researched data. All authors contributed to the discussion, and reviewed and edited the manuscript. MK and ZY are the guarantors of this work, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

None declared.

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