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Research letter

Lipoprotein(a) levels are doubled in left-handed patients with diabetes

Handedness is a tangible manifestation of cerebral motor lateralization. It is partly hereditary, it arises early in foetal life, and is modulated by intrauterine, perinatal and epigenetic factors. While the molecular bases of handedness have yet to be formally established, genetic studies have hinted at a polygenic origin partly under the control of molecular mechanisms establishing left–right body asymmetry. A previous report had found that non-right-handed (non-RH) patients with type 2 diabetes mellitus (T2DM) had better insulin sensitivity (IS) than their right-handed (RH) counterparts, which was unrelated to differences in obesity, body composition and physical activity. It was also observed that gastrointestinal intolerance to metformin was associated with a lower prevalence of ischaemic heart disease and with being left-handed (LH), whereas being non-RH was over-represented among metabolically-healthy normal-weight T2DM patients without the metabolic syndrome (MetS). Yet, there are virtually no data on lipids, lipoproteins or apolipoprotein (apo) levels as a function of motor laterality. For this reason, our present analysis was performed to determine whether laterality could modulate lipids/lipoproteins, including lipoprotein(a) [Lp(a)], in DM patients [1–8].

Our analysis of 517 Caucasian T2DM patients divided them into RH and non-RH (LH and ambidextrous) groups. Motor laterality was determined by their self-reported handedness, with non-RH being characterized by preferential use of the left hand or equal use of both hands for common tasks, with concordance between self-declared handedness and writing hand. Exclusion criteria included medications that could influence IS and β-cell function (other than for glucose-lowering), chronic inflammatory diseases, cancer and major organ failure. All patients provided their informed consent, and the study protocol was approved by the relevant Institutional Review Board.

Age, family history of DM and early-onset coronary heart disease (EOCHD), diabetes duration, smoking, ethanol intake, education level, leisure-time (LT) physical activity and time spent in front of screens, body mass index (BMI), blood pressure (BP), waist circumference (WC), fat mass, visceral fat and skeletal muscle were recorded. Methods used to determine MetS, atherogenic dyslipidaemia (AD) and micro-/macrovascular complications are described elsewhere [6]. In addition, β-cell function (B) and IS were assessed using updated homoeostasis model assessment (HOMA2): values of insulin secretion (B; normal: 100%) were plotted as a function of IS (S; normal: 100%) to determine the hyperbolic product area (B × S; unit: $\%^2$; normal: 100%, corresponding to $10^4\%^2$), representing residual β-cell function. Loss of hyperbolic product (B × S loss rate; % $year^{-1}$) was obtained by dividing 100% − (B × S) by age.

HbA1c levels, glycaemia and insulinaemia were determined from fasting samples, as were lipids and lipoproteins, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C; by Friedewald's formula), non-HDL-C, apoA-I and apoB100. In patients using lipid-modulating drugs (LMDs), pretreatment values were also documented. Lp(a) concentrations were determined by turbidimetric analysis (Tina-quant® Lp(a) Gen.2 assay, Roche Diagnostics International, Rotkreuz, Switzerland), with a threshold value >75 nmol/L to indicate increased cardiovascular (CV) risk, and the mean ± standard deviation (SD) reference value for Lp(a) was 42 ± 53 nmol L^{-1} [median: 10, interquartile range (IQR): 10–54 nmol L^{-1}, range: 5–245 nmol L^{-1}]; 20% of controls had Lp(a) values >75 nmol L^{-1}. From LDL-C levels, the amount of cholesterol within non-apo(a)-carrying LDLs (common LDLs) was calculated according to Li et al. [9] and reported as 'non-Lp(a) LDL-C'. Results are presented as means ± SD, medians (IQR) or proportions (%). Significance of differences was assessed using Student's *t*, Welch's and Fisher's exact tests, and results were considered significant for *P* values <0.05.

For all patients ($n = 517$), mean age was 68 ± 12 years and the gender (male/female) ratio was 62%/38%. A family history of diabetes and/or EOCHD was present in 47% and 12%, respectively. LMDs as statins (78%), fenofibrate (21%) and/or ezetimibe (14%) were used by 84% of patients; the within-statin distribution was simvastatin (47%), atorvastatin (26%), rosuvastatin (22%) and pravastatin (5%).

The proportion of RH and non-RH patients was 86% ($n = 444$) and 14% ($n = 73$), respectively. Within the non-RH group, LH represented 77% ($n = 56$) while 23% ($n = 17$) were ambidextrous. Patients' characteristics according to motor laterality are presented in Table 1. The two groups did not differ in age, gender, education levels, smoking, family history of DM and DM duration. However, a family history for EOCHD was 2.3-fold more prevalent in the non-RH group ($P = 0.0035$). RH and non-RH patients had similar values for HbA1c, estimated glomerular filtration rate (eGFR), microalbuminuria and micro-/macrovascular complications. The proportion of those with HbA1c < 7.0% was 37% in the RH *vs* 49% in the non-RH ($P = 0.0510$). Ethanol intake was similar between groups, as were LT physical activity and time spent in front of screens (data not shown).

There were also no differences between groups in BMI, hypertension, BP, WC, body composition, obesity distribution, MetS frequency/severity and presence of fatty liver or sleep apnoea. However, IS was 66% in the non-RHs, who were much less insulin-resistant than the RHs, whose IS was 52% ($P = 0.0133$), and this amounted to +14% (absolute) and +27% (relative) differences in IS between groups. Residual β-cell function (B × S) and (B × S loss rate) did not differ according to laterality, nor were there any observed differences in glucose-lowering and CV drug use, except for those treated with insulin (+43% in RHs) or receiving fenofibrate (+74% in non-RHs).

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Table 1
Characteristics of T2DM patients according to laterality.

		Right-handed	Non-right-handed	*P*
n		444	73	–
Age	years	69 (12)	66 (14)	NS
Male:female	%	61:39	68:32	NS
Family history of diabetes	%	47	45	NS
Family history of EOCHD	%	10	23	0.0035
Diabetes duration	years	17 (9)	15 (10)	NS
HbA1c	%	7.5 (1.3)	7.3 (1.2)	NS
	mmol mol^{-1}	58 (10)	56 (9)	NS
HbA1c < 7.0%	%	37	49	NS
eGFR	mL min^{-1} 1.73 m^2	73 (27)	74 (26)	NS
Micro-/macroalbuminuria	%	22/11	17/14	NS
macroangiopathy	%	34	41	NS
CAD – TIA/stroke – PAD	%	23 – 9 – 8	29 – 11 – 11	NS
Microangiopathy – DRP – PNP	%	46 – 23 – 24	41 – 14 – 22	NS
BMI	kg m^{-2}	29 (6)	29 (6)	NS
Waist circumference	cm	104 (15)	105 (16)	NS
Fat mass	%	31 (10)	30 (9)	NS
Visceral fat	0–30 score	13 (5)	12 (5)	NS
MetS	%	84	85	NS
Hepatic steatosis	%	74	74	NS
Insulin sensitivity	%	52 (36)	66 (45)	0.0133
Hyperbolic product [B × S]	%	26.8 (18.3)	29.4 (16.7)	NS
[B × S] loss rate	% year^{-1}	1.30 (0.51)	1.27 (0.43)	NS
MET – BCS – TZD – IBT	%	71 – 43 – 3 – 23	77 – 44 – 7 – 33	NS
Insulin	%	50	35	0.0226
Insulin dose	IU day^{-1} kg^{-1}	0.79 (0.67)	0.71 (0.63)	NS
Lipid-modifying drug(s)	%	84	86	NS
Statins – ezetimibe	%	78 – 14	75 – 16	NS
Low- and high-intensity statins	%	39 – 39	31 – 44	NS
Fenofibrate	%	19	33	0.0121
Total cholesterol	mg dL^{-1}	157 (34)	156 (36)	NS
Non-HDL-C	mg dL^{-1}	108 (34)	107 (35)	NS
Apolipoprotein B_{100}	mg dL^{-1}	85 (22)	86 (26)	NS
LDL-C[a]	mg dL^{-1}	77 (28)	78 (32)	NS
[Non-Lp(a) – LDL-C][b]	mg dL^{-1}	69 (30)	67 (33)	NS
Pre-statin LDL-C[c]	mg dL^{-1}	142 (34)	164 (51)	0.0030
On-statin LDL-C[c]	mg dL^{-1}	70 (22)	74 (29)	NS
Lipoprotein(a)				
Mean	nmol L^{-1}	48.6 (72.0)	72.5 (95.6)	0.0018
Median	nmol L^{-1}	18.7	37.0	
IQR [range]	nmol L^{-1}	9–63 [2–701]	11–85 [5–545]	
>75 nmol L^{-1}	%	20	32	0.0467
HDL-C	mg dL^{-1}	49 (17)	48 (16)	NS
Apolipoprotein A-I	mg dL^{-1}	148 (29)	149 (32)	NS
Triglycerides	mg dL^{-1}	164 (116)	149 (82)	NS
Atherogenic dyslipidemia	%	49	51	NS

Results are expressed as means (1 SD), median [interquartile range (IQR)], or proportions (%). BCS: beta-cell stimulant (sulphonylurea or glinide); BMI: body mass index; [B × S]: hyperbolic product between insulin sensitivity and beta-cell function; C: cholesterol; CAD: coronary artery disease; CHD: coronary heart disease; DRP: diabetic retinopathy; eGFR: estimated glomerular filtration rate; EOCHD: early-onset coronary heart disease; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; IBT: incretin-based therapies (dipeptidyl peptidase type 4 inhibitor or glucagon-like peptide 1 receptor agonist); LDL: low-density lipoprotein; Lp(a): lipoprotein(a); MET: metformin; MetS: metabolic syndrome; PAD: peripheral artery disease; PNP: polyneuropathy; TIA: transient ischaemic attack; TZD: thiazolidinedione.
[a] Calculated according to Friedewald's formula.
[b] Calculated according to Li et al.
[c] Friedewald's formula in *n* = 348 (right-handed) and *n* = 55 (non-right-handed) patients; NS: not significant.

Type of statins and dosages as well as the proportions receiving low- *vs* high-intensity statins did not differ according to laterality. Likewise, routine lipids were similar in both groups, as were apoB100, non-Lp(a) LDL-C, apoA-I, AD prevalence/severity and LDL-particle size. In statin-treated patients, pretreatment LDL-C was higher by 22 mg/dL in non-RHs (+15%; $P = 0.0030$), and a subanalysis excluding fibrate users showed that pretreatment LDL-C was also higher (+14%) in non-RHs. LDL-C with statin use was, on the other hand, similar between groups.

For all patients ($n = 517$), mean and median Lp(a) values were 52 ± 76 and 22 nmol L^{-1} (IQR: 10–66, range: 2–701 nmol L^{-1}), respectively, and 22% had Lp(a) > 75 nmol L^{-1}. There was also a substantial difference between RHs and non-RHs in Lp(a), with median levels markedly and significantly higher (+98%) in non-RHs, with an absolute difference of 18.3 nmol L^{-1} ($P = 0.0018$). Such an increase represented an overall upward shift of Lp(a) in the latter. Thus, almost one in three (32%) non-RH patients had a pathological amount (> 75 nmol L^{-1}) of this specific LDL compared with only one in five RH patients ($P = 0.0467$). Among non-RHs, Lp(a) was increased to a greater extent in LH compared with ambidextrous patients [median: 41 *vs* 30 (IQR: 10–88 *vs* 23–73) nmol L^{-1}, respectively], and the proportion of pathological Lp(a) levels was greater in LH than in ambidextrous patients (34% *vs* 24%, respectively). On considering all patients, non-RHs were over-represented (1 out of 5) among those with pathological Lp(a) values ($n = 114$), compared with a 12% frequency of RH patients among those with normal Lp(a) levels ($n = 403$; $P = 0.0467$), amounting to 8% (absolute) and 67% (relative) more non-RH patients among hyper-Lp(a) patients (data not shown).

The present study has characterized lipids, lipoproteins and apolipoproteins as a function of motor laterality in T2DM. There was a marked and significant difference in Lp(a) between RH and non-RH patients, with the latter having nearly twice the amount of

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this particular lipoprotein. As a rule, Lp(a) levels are highly variable between individuals, as they are under the strong genetic control of *LPA*, the apo(a) gene. Thus, the higher Lp(a) levels in the non-RHs was unexpected, and even more so as the other routine lipids and lipoproteins were not increased. Furthermore, being non-RH was much more common among patients with elevated Lp(a), while ambidextrous patients, whose laterality overlaps both RHs and LHs, also showed elevated Lp(a) *vis-à-vis* RHs, albeit with less intensity than in LHs, thereby suggesting the presence of a biological gradient between Lp(a) and motor laterality.

Laterality is set early in life, as areo Lp(a) levels, and is already determined in pregnancy/childhood. However, it was totally unexpected that non-RHs would have higher Lp(a) levels than RHs, and it is not yet known whether such selective dyslipidaemia is limited to DM patients. In any case, three hypotheses can be proposed: (i) higher Lp(a) levels might increase a given subject's probability of being non-RH or *vice versa*; (ii) being non-RH might result in a secondary rise in Lp(a), albeit an improbable scenario based on *LPA* gene regulation and Lp(a) physiology; and (iii) as yet unidentified factors might simultaneously increase both Lp(a) and the odds of being LH [8,10].

Lp(a) measurement in our study was based on molarity, not on mass. Thus, the elevated Lp(a) in non-RH patients corresponds to an increased number of LDL Lp(a) particles, irrespective of any differences in apo(a) between LH and RH patients. The greater number of Lp(a) particles in non-RHs could result from: (i) increased production of LDL-like particles to subsequently bind to apo(a); (ii) increased synthesis of the latter; (iii) enhanced extracellular assembly of Lp(a) components or their decreased prefusion catabolism; and (iv) increased uptake of Lp(a), especially by the liver.

Lp(a) is only barely modulated by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and RH patients should respond just like non-RH patients regarding LDL-C relative reductions while taking statins. Higher Lp(a) levels contribute to boosting pre-statin LDL-C in non-RHs. Yet, on-statin LDL-C was unaffected by laterality, suggesting a greater response to LMDs in non-RHs even when they were not treated more intensively. Nevertheless, it cannot be excluded, despite nothing to suggest it either, that further LDL-C-lowering in non-RHs reflects better compliance to LMDs, as the effect of fibrates, which were more often used in non-RHs, was ruled out.

Ultimately, LDL-C levels in treated and untreated patients did not differ by laterality, even after being adjusted for the confounding effect of within-Lp(a) cholesterol. This possibility of an enhanced response to statins in non-RHs is noteworthy as, after adjusting for higher Lp(a) levels, these patients had a statin-responsive cholesterol pool (non-Lp(a) LDL-C) similar to that in RH patients. Moreover and despite higher IS, non-RHs showed neither lower TG-rich lipoprotein levels nor AD prevalence/severity.

Among the non-lipid differences, a more-than-doubled frequency of EOCHD was identified in non-RH patients' relatives, with less frequent use of insulin. This marked difference in EOCHD may be partly related to Lp(a) heritability, as intrafamilial Lp(a) is strongly determined by the apo(a) gene [7,8], whereas the smaller percentage of patients treated with insulin could be related to higher IS which, for any given β-cell deficit, could help to postpone insulin therapy.

Our study has some limitations. Our data came from Caucasians only and therefore cannot be extended to other DM or general populations. Also, while LDL-C was calculated according to Friedewald's or Lp(a)-adjusting formulas, there was no determination of particle-size differences between RHs and non-RHs for apo(a), nor were apo(a) isoforms, kringle-IV type-2 (KIV-2) repeats or apo(a) alleles characterized. Finally, the cross-sectional design of our study cannot assess whether Lp(a) variability translates into different micro-/macrovascular outcomes.

In conclusion, our analysis of motor laterality and lipids in T2DM has serendipitously allowed the observation that non-RH patients have levels of Lp(a) that are twice those of RH patients. Although this finding requires confirmation in other populations, it could generate novel hypotheses on the cause–effect relationships between lipids, lipoproteins and motor laterality.

Ethical approval

Ethics approval and consent were given by the Commission of Biomedical Ethics Hospital – Faculty of the Catholic University of Louvain in Brussels (B403-2017-16NOV-521).

Study data are available at the Division of Endocrinology & Nutrition, Cliniques universitaires St-Luc and Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels (Belgium) (person of contact: Prof. M.P. Hermans).

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Authors' contributions

All authors contributed equally to the research and preparation of the manuscript. All of the type 2 diabetes patients studied were followed consecutively by the corresponding author (M.P.H.). All authors read and approved the final version of the manuscript for publication.

Disclosure of interest

The authors declare that they have no competing interest.

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