CLINICAL STUDY

Low-density lipoprotein apolipoprotein B100 turnover in hypopituitary patients with GH deficiency: a stable isotope study

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Abstract

Background: Epidemiological studies suggest that hypopituitary patients have an increased risk for cardiovascular mortality. The dyslipidaemia associated with this condition is often characterised by an increase in total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol (LDL-C) and may contribute to these findings. The underlying mechanisms are not fully elucidated.

Materials and Methods: LDL apolipoprotein B (apoB) production rate and metabolic clearance rate were measured in seven patients with hypopituitarism (including GH deficiency) under stable conventional replacement therapy (three males and four females; age 40–16.1 years; body mass index 29.0–6.1 kg/m² (means±s.d.)) and seven age-, gender- and body mass index-matched control subjects with an infusion of 1-¹³C-leucine. Fasting lipid profile and lipid composition of LDL were also measured. **Results:** Fasting TC, triglycerides (TG), high-density lipoprotein-C, LDL-C and free fatty acid concentrations were not different between hypopituitary patients and control subjects. LDL-TG ($P < 0.006$) and LDL-TG/LDL apoB ratio ($P < 0.02$) were significantly increased in hypopituitary patients. LDL apoB pool size was not statistically different between patients and control subjects. In the hypopituitary patients, LDL apoB metabolic clearance rate ($P < 0.05$) and LDL apoB production rate ($P < 0.02$) were lower than in the control subjects.

Conclusions: The present results suggest that LDL apoB turnover and LDL composition is altered in hypopituitary patients. Whether these findings explain the increased risk for cardiovascular disease in hypopituitary patients remains to be established.

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Introduction

Epidemiological studies suggest that hypopituitary subjects have an increased risk for cardiovascular mortality (1–3). It is tempting to speculate that the dyslipidaemic condition often associated with this condition contributes to premature atherosclerosis. Although most of the studies have demonstrated elevated low-density lipoprotein (LDL) concentrations (4–6) or hypertriglyceridaemia and reduced high-density lipoprotein cholesterol (HDL-C) concentrations (6), some investigators did not confirm dyslipidaemia in hypopituitary patients (7).

The atherogenic potential of LDL particles depends not only on the quantity (i.e. concentrations) but also on their quality and kinetic behaviour. Triglyceride (TG) enrichment of LDL particles is associated with small,

dense LDL particles which are known to be particularly atherogenic (8, 9). There is evidence that LDL particle size is decreased in patients with childhood-onset of growth hormone (GH) deficiency (10) and in adult hypopituitarism (11); this may impact on cardiovascular risk.

GH deficiency may play an important role in the dyslipidaemic condition since hepatic LDL receptor expression has been shown to be modulated by GH *in vitro* (12), in animal models (13) and in humans (14). Consistent with these findings, a substantial number of studies have shown that GH replacement therapy resulted in a significant reduction in total and LDL cholesterol (LDL-C) concentrations (15–19), although some reports did not find a significant change (20, 21). Short-term GH replacement therapy persistently failed to decrease hypertriglyceridaemia (22), probably because of the GH-induced increase in insulin resistance (22).

There are few studies investigating the kinetics of apolipoprotein B100 (apoB)-containing lipoproteins in hypopituitary patients. Recent data from very low-density lipoprotein (VLDL) apoB turnover studies in hypopituitary patients using stable isotope techniques suggest that the VLDL apoB secretion rate is increased (6, 7) and VLDL catabolism is decreased (6). These findings may contribute to the dyslipidaemic conditions of hypopituitary adults. However, it is currently not known whether LDL apoB metabolism is impaired in hypopituitary adults.

We therefore aimed to test the hypothesis that LDL apoB turnover is impaired in hypopituitary patients under conventional replacement therapy (without GH). Impaired LDL apoB metabolism, may in turn, contribute to the dyslipidaemic condition of these patients. Using a stable isotope technique, LDL apoB kinetics was investigated in seven hypopituitary patients with GH deficiency and in seven age-, sex- and body mass index (BMI)-matched healthy control subjects. In addition, fasting lipid profile and LDL composition were assessed.

Materials and methods

Patients

Seven patients with hypopituitarism and GH deficiency (four women and three men) and seven age-, gender- and BMI-matched healthy control subjects volunteered for the study. The clinical characteristics of these patients are summarised in Table 1. All patients had multiple pituitary deficiencies, had suffered from GH

deficiency for at least 1 year and were receiving stable conventional replacement therapy. GH deficiency was defined as a peak GH of less than 3 mU/l during an insulin provocation test with nadir plasma glucose less than 2.2 mmol/l. None of the patients or control subjects had diabetes mellitus, abnormal liver function or were taking drugs known to affect lipid metabolism. All patients provided informed written consent and the study was approved by St Thomas' Hospital Ethics Committee.

Study protocol

Identical metabolic investigations were performed in the patients and the control subjects. They were admitted to the metabolic ward at 0830 h after a 12-h overnight fast. Body weight was measured on an electronic balance with subjects wearing light clothes and without shoes. Height was assessed by a stadiometer. They were studied in a semi-recumbent position and allowed to drink water. An indwelling cannula was placed in a superficial vein of the antecubital fossa for administration of the stable isotope tracer and another in the contralateral arm for blood sampling. At the beginning of the study, 10 ml EDTA plasma was collected for measurement of total cholesterol (TC), triglyceride (TG), HDL-C and ultracentrifugation of lipoproteins. 1-¹³C-Leucine (15 mg/ml, ¹³C enrichment 99%; Tracer Technologies, Sommerville, MA, USA) was administered as a primed (1 mg/kg) constant infusion (1 mg/kg per h) for 9 h. Blood samples (5 ml) were taken into EDTA tubes for LDL apoB enrichment at

Table 1 Clinical characteristics of the hypopituitary patients with GH deficiency and control subjects.

									Hormone deficiencies			
Subject no.	Age (years)	Gender	BMI (kg/m ²)	ApoE phenotype	Diagnosis	Surgery	DxRT	Duration of hypopituitarism (years)				
									G	T	A	D
Hypopituitary patients												
1	36	F	22.4	E2/E3	Menigioma	+	+	6	+	+	+	
2	24	M	29.6	E3/E3	Cushing's syndrome	+		7	+	+	+	
3	23	M	22.6	E3/E3	Traumatic			11	+	+	+	
4	67	F	27.5	E3/E3	Non-secreting adenoma	+	+	14			+	+
5	52	F	31.2	E3/E3	Non-secretine adenoma	+	+	27	+	+	+	
6	33	F	40.3	E3/E3	Craniopharyngioma	+	+	12	+	+	+	+
7	47	M	29.7	E3/E3	Prolactinoma			2	+			
Mean±s.d.	40±16.0	4F/3M	29.0±6.1					10.3±8.0				
Control group												
8	40	F	23.3	NA								
9	23	M	31.0	NA								
10	23	M	24.7	NA								
11	67	F	31.3	E3/E3								
12	52	F	21.0	E3/E3								
13	43	F	47.1	E3/E4								
14	46	M	28.5	E3/E3								
Mean±s.d.	42±15.6	4F/3M	29.6±8.7									

DxRT, pituitary irradiation. Hormone deficiencies: G, gonadal; T, thyroxine; A, adrenal; D, antidiuretic hormone. NA, not available.

baseline and at 30-min intervals throughout the study. Blood samples (5 ml) were taken into lithium heparinised tubes at baseline and after 15, 30, 45, 60, 120, 240, 360, 480 and 540 min to determine ^{13}C enrichment of α -ketoisocaproate (α -KIC), the deaminated product of leucine that provides a measure of intracellular leucine enrichment (21). At baseline and after 2, 6 and 9 h of infusion, 10 ml blood samples were collected into an EDTA (0.34 mol/l) tube to determine LDL-TG, LDL-C and LDL apoB concentrations. Because of the reduced extracellular volume in hypopituitary patients plasma volume was measured by a standardised radionuclide dilution technique (23). In the control subjects, plasma volume was calculated as 4.5% of body weight in men and 4.3% in women; this has previously been shown to give a good estimate of plasma volume in healthy subjects (24–26).

Isolation and measurement of isotopic enrichment of LDL apoB

The detailed protocol is outlined elsewhere (19). Briefly, following removal of VLDL and intermediate density lipoprotein (IDL) by sequential floatation ultracentrifugation, LDL was isolated after ultracentrifugation (Beckham Coulter Optima LE80-K, High Wycombe, Bucks, UK) for 20 h at an adjusted density of 1.063 kg/l. ApoB was precipitated by the tetramethyl-urea method (27). The precipitate was delipidated using ether-ethanol solution and the delipidated apoB precipitate hydrolysed in 6 M hydrochloric acid (19). Samples were derivatised to their N-acetyl, n-propyl-ester derivatives (28) and analysed on a Sira series 2 isotope ratio mass spectrometer (VG Instruments, Altringham, Cheshire, UK) coupled to an Orchid gas chromatograph interface module (Europa Scientific, Crewe, Cheshire, UK). The gas chromatograph was equipped with an AT-1 capillary column (60 m, 0.25 mm internal diameter, 1.0 μm film thickness; Alltech, Carnforth, Lancashire, UK). The carrier gas was helium and the column head pressure was set to 22 psi. The injector temperature was set to 250 °C. For sample analysis, the column was held isothermally at 70 °C for 1 min, then programmed to increase at 20 °C/min up to 200 °C, 3 °C/min from 200 to 250 °C, 30 °C/min from 250 to 300 °C and was held at 300 °C for 5 min. Isotope abundance was expressed relative to pulse peaks of reference CO_2 gas. Data were analysed using the manufacturer's software.

Quantification of LDL apoB and other analytes

LDL apoB concentration was determined by a modified Lowry method (inter-assay coefficient of variation (CV) 4%; (29)). Plasma TC and TG concentrations were measured by an enzymatic method (Boehringer Mannheim, Mannheim, Germany) using a Cobas Fara

II analyzer (Roche, Welwyn Garden City, Herts, UK). HDL-C was separated by precipitation of apoB-containing lipoproteins with dextran sulphate/magnesium chloride and measured enzymatically. LDL-C was measured enzymatically (Boehringer Mannheim) after isolation by ultracentrifugation. Plasma free fatty acids (FFA) concentrations were measured enzymatically (FFA kit; Wako Chemicals GmbH, Neuss, Germany; interassay CV 3.6%). Apolipoprotein E phenotype was determined by isoelectric focusing (19).

Qualitative changes within the LDL particles were assessed by calculating the molar ratio of LDL-TG/LDL apoB and LDL-C/LDL apoB. In particular, an increase in TG content within the LDL particles has been associated with small dense LDL particles (30) that are known to be easily oxidised and catabolised by the scavenger receptor, resulting in an augmented pro-atherogenic potential (30).

Calculation of LDL apoB secretion and clearance rate

LDL apoB enrichment with ^{13}C -leucine was calculated using a simple linear regression model. The precursor compartment for the incorporation of ^{13}C -leucine into the LDL particles was the steady-state tracer/tracee of α -KIC. The catabolic rate of LDL from plasma is expressed as fractional appearance rate (FAR) and catabolic rate (FCR). Throughout the study the patients were in steady-state as shown by constant LDL apoB concentrations (data not shown). In this case, FAR equals FCR. A total of 11 time-points over the 9-h tracer infusion was included in the linear regression model.

The absolute LDL apoB production rate (PR) was calculated as the product of FCR and the LDL apoB pool size divided by body weight. Pool size was determined as the product of plasma volume and LDL apoB concentration taken as the mean of four samples taken during the study and metabolic clearance rate (MCR) was calculated as the product of FCR and plasma volume.

Data presentation and statistics

Normally distributed data (age, BMI) are described using the mean and s.d. All kinetic data were not normally distributed and are described using the median and the interquartile range. Parametric data were analysed using unpaired Student's *t*-test. Non-parametric testing (Mann–Whitney) was performed to analyse kinetic data. Statistical significance is assumed at a 5% level.

Results

Patients

The clinical characteristics of the patients and control subjects are summarised in Table 1. They were well matched in terms of age, gender and BMI.

Lipid profile

The fasting lipid profile of the patients and control subjects is summarised in Table 2. Fasting TG concentrations in hypopituitary patients with GH deficiency were increased without statistical significance ($P = 0.11$). TC, LDL-C, HDL-C and FFA concentrations were not different compared with the control subjects.

LDL composition

The LDL composition of the patients and the matched control subjects is summarised in Table 3. There was a significant 1.8-fold increase in LDL-TG ($P < 0.006$) mirrored by a 1.6-fold increase in the ratio of LDL-TG/LDL apoB in the hypopituitary patients compared with the matched control subjects ($P < 0.02$). LDL apoB and LDL-C content of LDL particles were not significantly different.

Kinetic characteristic of LDL apoB metabolism (Table 4)

LDL apoB kinetics were in a steady-state supported by the fact that LDL apoB concentrations did not show a significant change at the selected time-points throughout the study (data not shown). Precursor pool enrichment as measured by ^{13}C - α -KIC occurred rapidly and remained constant throughout as shown in previous studies (19).

There was a tendency for a reduced plasma volume in hypopituitary patients with GH deficiency ($P = 0.05$) whereas LDL apoB pool size ($P = 0.31$) and LDL apoB FCR ($P = 0.12$) were not significantly different. LDL apoB MCR ($P < 0.05$) and LDL PR ($P < 0.02$) were decreased in the hypopituitary patients compared with the control subjects.

Discussion

This is the first study that has compared LDL metabolism in hypopituitary patients with GH deficiency with age-, sex- and BMI-matched control subjects. In the hypopituitary patients, LDL apoB MCR and LDL

apoB PR were lower than in the control subjects. There was no difference in LDL apoB pool size between groups but there was a significant increase in LDL-TG content in patients compared with the control subjects.

Fasting lipid profile was not significantly different between the hypopituitary patients and control subjects. This is in contrast to most of the previous studies with a large sample size (17, 31, 32). In the hypopituitary patients of the present study mean TC, LDL-C and TG concentrations were increased by 10%, 12% and 55% respectively and HDL-C levels were reduced by 7% compared with the control subjects, suggesting a trend for an impaired lipid profile. It is likely, therefore, that the small sample size of the current investigation has led to the statistically not significant differences in fasting lipid profile. Alternatively, differences in dietary fat intake as well as dissimilar genetic backgrounds may have contributed to these results.

Traditional risk factors for coronary artery disease – such as elevated total cholesterol and LDL-C concentrations, hypertension, nicotine abuse, decreased HDL-C concentrations, diabetes and a family history of coronary heart disease predict only about 50% of the risk of developing the disease (33). This suggests that 'non-traditional' risk factors contribute to the pathogenesis of the disease. Amongst them, qualitative changes within the LDL particles appear to be of particular importance (30). The present data have shown an increase in TG content within the LDL particles, which has been associated with small dense LDL particles (30). Small dense LDL particles are known to be easily oxidised and catabolised by the scavenger receptor, resulting in an augmented pro-atherogenic potential (30). Similar compositional changes were reported in patients with childhood-onset GH deficiency (10), suggesting that the hypopituitary condition may contribute to the TG enrichment within the LDL particles. By assessing LDL particle size, O'Neal *et al.* (11) have demonstrated an increase in the number of small dense LDL in hypopituitary patients with GH deficiency, in keeping with the present findings. In addition, previous studies have demonstrated a significant increase in TG within the VLDL fraction in hypopituitary patients (6, 34). An augmented content of TG within the VLDL fraction is known to be associated with an increase in small dense LDL (35), which further supports our findings. An increase in small dense LDL is well known in insulin-resistant conditions (35). Insulin resistance, in turn, is a characteristic feature of hypopituitary patients with GH deficiency (36). It is conceivable, therefore, that the present findings may be related to the insulin-resistant condition of the patients.

We (6) and others (7) have previously shown that VLDL PR is increased in hypopituitary patients whereas VLDL catabolism is similar (7) or reduced in hypopituitary patients (6). If we assume that LDL production is mainly due to delipidation of VLDL particles (VLDL

Table 2 Fasting lipid profile of hypopituitary patients with GH deficiency and control subjects. Values are means $\pm$ S.D.

	Plasma				
	TC (mmol/l)	LDL-C (mmol/l)	HDL-C (mmol/l)	TG (mmol/l)	FFA (mmol/l)
Hypopituitary patients	5.3 $\pm$ 0.7	2.8 $\pm$ 0.5	1.4 $\pm$ 0.4	1.4 $\pm$ 0.7	0.83 $\pm$ 0
Control subjects	4.8 $\pm$ 0.5	2.5 $\pm$ 0.5	1.5 $\pm$ 0.3	0.9 $\pm$ 0.3	0.58 $\pm$ 0
<i>P</i> value	0.19	0.62	0.70	0.11	0.16

Unpaired *t*-test was performed. Differences in TG concentrations were analysed after log transformation.

Table 3 LDL composition in hypopituitary patients with GH deficiency and control subjects. Values are means $\pm$ S.D.

Subject no.	Plasma				
	LDL-C (mg/l)	LDL-TG (mg/l)	LDL apoB (mg/l)	LDL-C/apoB	LDL-TG/apoB
Hypopituitary patients					
1	847.5	183.8	492.0	1.72	0.37
2	1041.0	218.8	680.0	1.53	0.32
3	1013.9	131.3	413.0	2.46	0.32
4	1048.8	218.8	499.1	2.10	0.44
5	1346.8	315.0	519.0	2.59	0.61
6	909.5	262.5	470.0	1.94	0.56
7	1277.1	323.8	686.0	1.86	0.47
Mean (S.D.)	1069.2 (182.2)	236.3 (69.5)	537.0 (105.1)	2.03 (0.38)	0.44 (0.11)
Control subjects					
8	769.70	161.39	370.00	2.08	0.44
9	671.66	70.00	350.00	1.92	0.20
10	871.18	91.39	480.00	1.81	0.19
11	1157.13	140.00	514.00	2.25	0.27
12	1222.92	192.50	488.40	2.50	0.39
13	963.63	148.75	587.00	1.64	0.25
14	1048.77	131.25	550.70	1.90	0.24
Mean (S.D.)	957.9 (201.3)	133.6 (41.5)	477.2 (88.2)	2.02 (0.29)	0.28 (0.10)
P value	0.62	<0.006	0.45	0.90	<0.02

Unpaired *t*-test was performed.

catabolism (37)) the present finding of a decrease in LDL apoB PR would be consistent with these previous studies (6, 7). GH has been shown to regulate hepatic LDL receptor expression in rats (13), *in vitro* in normal and in hepG2 cells (12) and in humans (38). The LDL receptor is critical for the uptake of small VLDL and LDL particles (37). It is conceivable, therefore, that the GH-deficient condition of the hypopituitary patients contributes to a reduced direct uptake of VLDL and LDL particles, thereby explaining the reduced VLDL catabolism in our previous study (6) and the reduced LDL

catabolism in the present study. The finding that GH replacement therapy results in an increase in VLDL (19) and LDL apoB catabolism (39) further substantiates the hypothesis that GH status might be critical for apoB-containing lipoprotein metabolism (Fig. 1). Alternatively, it is well known that hypopituitary patients with GH deficiency tend to present with reduced blood volumes (40) which, in turn, impacts on cardiovascular performance (41) and, therefore, on metabolic turnover studies. A reduced cardiovascular performance is associated with reduced interactions between LDL

Table 4 Kinetic characteristics of LDL apoB metabolism in hypopituitary patients with adult GH deficiency and control subjects. Data are expressed as median and interquartile range (IQR).

Subject no.	PV (l)	LDL apoB pool (mg)	LDL apoB FCR (pools/day)	LDL apoB PR (mg/kg per day)	LDL apoB MCR (ml/min)
Hypopituitary patients					
1	2.2	992.9	0.47	8.0	0.72
2	2.5	1108.8	0.39	5.4	0.68
3	3.6	1337.8	0.43	7.6	1.08
4	2.3	1080.5	0.35	5.2	0.56
5	2.9	1691.6	0.06	1.4	0.12
6	2.5	1105.8	0.41	4.6	0.71
7	3.4	2140.3	0.24	6.2	0.57
Median (IQR)	2.5 (2.4–3.2)	1108.8 (1093.1–1514.7)	0.39 (0.30–0.42)	5.4 (4.9–6.9)	0.68 (0.56–0.71)
Control subjects					
8	2.9	1076.4	0.54	8.5	1.10
9	3.5	1233.4	0.50	7.5	1.22
10	3.5	1681.9	0.45	9.3	1.09
11	3.3	1700.6	0.49	10.9	1.11
12	2.5	1173.5	0.29	5.8	0.51
13	5.0	2866.0	0.41	10.1	1.42
14	3.9	2094.5	0.39	8.9	1.07
Median (IQR)	3.5 (3.1–3.7)	1681.9 (1203.4–1897.5)	0.45 (0.40–0.49)	8.9 (8.0–9.7)	1.10 (1.08–1.17)
P value	0.052	0.31	0.12	<0.02	<0.05

PV, plasma volume. Non-parametric test (Mann–Whitney test) was used for comparison.

Figure 1 This figure summarises the current knowledge on VLDL and LDL apoB metabolism in hypopituitary patients. The VLDL apoB turnover study has previously been published and has been included in the Figure (6, 7) VLDL particles are synthesised by the liver, secreted in the circulation and delipidated to form LDL particles that, in turn, are taken up by the liver or the peripheral tissues (37). In healthy control subjects, the delipidation cascade (open arrows) is functioning normally resulting in a normal VLDL and LDL apoB pool size (open circles). In contrast, in hypopituitary patients, VLDL apoB pool size (solid circle) is increased due to an increase in VLDL production (solid arrow) (6, 7) in combination with a reduced VLDL catabolism (6). The present study suggests that LDL apoB pool size (solid circle) in hypopituitary patients is similar to control subjects despite a decrease in LDL MCR (broken arrow). This is mainly related to a reduction in LDL production (i.e. VLDL catabolism (broken arrow)).

particles and their corresponding receptors, thereby contributing to a decrease in LDL turnover. The present data do not allow us to distinguish whether the performance of the cardiovascular system or differences in LDL receptor status are responsible for the present findings. However, it is established that exercise performance is reduced by 10–20% in hypopituitary patients with GH deficiency (22). GH replacement therapy has consistently been shown to improve exercise capacity (41, 42), probably because of an increase in preload (40), afterload (43, 44) and possibly a direct effect on the cardiac muscle (45). It is conceivable, therefore, that GH status may be important in the context of metabolism, not only through its effect on LDL receptor expression but also by its impact on the cardiovascular system. Finally, it cannot be excluded that the underlying pituitary disease and the concomitant hormone deficiencies, which are not replaced in a physiological and individualised manner, may significantly impact on apoB metabolism (46–48).

In view of the similar fasting lipid profile and unchanged LDL apoB pool size it remains to be established whether LDL apoB metabolism is the most important factor explaining the increase in cardiovascular mortality in hypopituitary patients. In particular 'non-traditional' risk factors involved in the pathogenesis of atherosclerosis, such as inflammatory markers (49, 50) and matrix-metallo-proteinases (MMP) activity (51), have been shown to be increased and endothelium function impaired (52, 53) in hypopituitary patients. Although long-term GH replacement therapy has been shown to result in persistent beneficial effects on the fasting lipid profile (54), the degree of improvement remains moderate at the GH replacement dose which is actually prescribed. In contrast, recent data suggest that there is a significant impact of GH replacement therapy on inflammatory

markers (49, 50), MMP activity (51) and endothelial function (43, 44, 55). Further studies are therefore warranted in order to investigate the role of lipid metabolism in relation to the 'non-traditional' cardiovascular risk factors in hypopituitary patients.

Assessment of distribution volume of a given metabolite (i.e. LDL apoB) is critical in estimating the kinetics of this metabolite. The distribution volume of LDL apoB is identical to the plasma volume. Plasma volume has been shown to be reduced in patients with hypopituitarism (40), possibly due to the concomitant GH deficiency (22) and has, therefore, been measured in the present investigation. In healthy subjects, plasma volume estimation based on body weight is a widely accepted method (26, 56). In the present study, no significant difference in LDL apoB pool size could be detected. In addition, based on previous studies where plasma volume was measured and calculated (6, 25), the differences between measured and calculated plasma volume were less than 10%, which would not significantly influence the present results.

There are several mathematical models to fit leucine enrichment data of apoB-containing lipoprotein turnover studies. These models try to estimate different metabolic pathways (i.e. direct uptake of VLDL or IDL vs delipidation to form LDL) of apoB-containing lipoproteins (57). The focus of the present study was the investigation of LDL metabolism only. We do not have any IDL enrichment data. Therefore it was not possible to apply a multicompartmental model and a simple mathematical approach (linear regression) was used to calculate production and catabolic rate of LDL apoB (58). The accuracy of linear regression depends on the number of time-points during the study (58). In the present study, a total of 11 time-points was obtained and the enrichment data resulted in a near linear curve in each patient. In this case, a linear regression model appears

to be adequate to fit the data. In addition, the absolute values of the kinetic parameters calculated by a multi-compartmental model in patients with impaired LDL catabolism were very similar to the present data (59), further substantiating our approach.

In summary, the present findings suggest that hypopituitary patients with GH deficiency have an impaired LDL apoB metabolism and an altered LDL composition. Whether these findings explain the increased risk for cardiovascular disease in hypopituitary patients remains to be established.

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