reports, but the level of evidence in the current study is higher.

A number of studies which reported therapeutic efficacy of LDL-A have been accumulated so far and those studies intended mostly for patients with FSGS. Although there have been several reports which showed therapeutic efficacy of LDL-A in patients with non-FSGS, most of them were case reports or case series with limited numbers of patients [12, 13]. However, in the POLARIS study, nearly half of the patients and the episodes registered in the study were non-FSGS and interestingly no significant difference of therapeutic effect was observed between FSGS and non-FSGS.

Table 4 Change of urinary protein before and after LDL-A treatment for each primary disease

Primary diseases	n[a]	Before	After
Focal segmental glomerulosclerosis	26	6.47 ± 2.98	3.26 ± 3.13
Membranous nephropathy	4	8.97 ± 2.29	6.95 ± 6.48
Henoch-Schönlein purpura nephritis	3	6.67 ± 4.50	3.15 ± 1.43
Minimal change nephrotic syndrome	2	1.96 ± 0.06	2.70 ± 3.13
Renal amyloidosis	2	5.45 ± 1.92	6.32 ± 2.52
IgA nephropathy	1	1.29	0.44
Membranoproliferative glomerulonephritis	1	4.60	1.85
Crescentic glomerulonephritis	1	3.81	0.61
Lupus nephropathy	1	8.79	0.13
Hepatitis B virus-associated nephropathy	1	8.90	3.91
non-FSGS	16	6.13 ± 3.41	3.89 ± 4.01

[a] Episodes with not specified primary disease were excluded

From reviewing previous reports, several possible mechanisms have been proposed for the beneficial therapeutic effect of LDL-A. Firstly, direct lowering of serum lipids including LDL, oxidized LDL, and VLDL was reported to contribute to regression of glomerular injury [14, 15]. Secondly, LDL-A is known to remove pathogenic factors other than noxious lipids. LDL-A can improve hypercoagulability by reduction of coagulation factors including von Willebrand's factor and fibrinogen [16, 17], and can also improve renal hemodynamics by reducing vasoconstrictive eicosanoids such as thromboxane A2 and increasing prostaglandin I2 [9]. Thirdly, it is conceivable that LDL-A should help with improvement of therapeutic effect of antiproteinuric drugs including steroids and/or calcineurin inhibitors because bioavailability of those drugs is known to be impaired under hyperlipidemic condition [18–20]. Enrollment in the current study required a patient to be resistant to medication; and therefore, steroids and/or CsA were administered in almost all episodes concomitantly with LDL-A. In contrast, Stenvinkel et al. [21] showed that LDL-A was effective for improving the condition of NS patients with hypercholesterolemia without any additional medication. However, a clear effect of LDL-A was not observed until 6 weeks after treatment, whereas the clinical effect in our study emerged immediately after or even during LDL-A treatment. Therefore, it is likely that improvement due to the effects of concomitant steroids or CsA contributed to the short-term clinical efficacy of LDL-A.

In addition to above-mentioned mechanisms for exerting the therapeutic effect, factors that affect the clinical efficacy of LDL-A were examined based on the results obtained in this study. The level of serum total protein at pre-treatment and duration of NS before the treatment were significantly affected by the efficacy ($p = 0.049$, 0.012,

Table 5 Serum and urine parameters at pre-treatment in effective and non-effective episodes

Clinical parameter	Unit	Effective	n	Non-effective	n	p-value
Serum total protein (SP)	(g/dL)	4.60 ± 0.67	25	4.20 ± 0.66	21	0.049
Serum albumin (SA)	(g/dL)	2.27 ± 0.57	25	2.03 ± 0.68	22	0.200
Serum creatinine (SCr)	(mg/dL)	1.48 ± 1.27	25	2.22 ± 1.86	22	0.117
Creatinine clearance (CCr)	(mL/min)	65.34 ± 45.13	13	71.71 ± 44.51	10	0.385
estimated glomerular filtration rate (eGFR)	(mL/min/m^2)	52.33 ± 26.12	25	44.14 ± 35.94	22	0.381
Urinary protein (UP)	(g/day)	5.56 ± 2.64	25	7.10 ± 3.15	22	0.075
Triglyceride (TG)	(mg/dL)	260.55 ± 175.58	22	265.59 ± 129.87	18	0.920
Total cholesterol (TC)	(mg/dL)	342.20 ± 99.71	20	324.00 ± 127.31	20	0.618
LDL cholesterol (LDL-c)	(mg/dL)	207.90 ± 94.14	20	203.46 ± 111.09	18	0.432
HDL-cholesterol (HDL-c)	(mg/dL)	72.08 ± 18.80	20	65.76 ± 27.44	14	0.895
Fibrinogen (Fb)	(mg/dL)	347.06 ± 109.53	16	413.34 ± 149.69	12	0.187
Thrombin-antithrombin III complex (TAT)	(ng/mL)	20.39 ± 40.84	12	8.38 ± 7.31	6	0.491

Table 6 Patient and episode characteristics of effective and non-effective episodes

Patient and episode characteristics	Effective	*n*	Non-effective	*n*	*p*-value
Age (years)	55.57 ± 19.09	23	55.20 ± 15.36	20	n.s.[a]
BMI	24.01 ± 5.55	24	22.76 ± 4.15	16	n.s.[a]
Average number of LDL-A sessions	9.52 ± 2.55	25	9.77 ± 12.72	22	n.s.[a]
Average frequency of LDL-A sessions (per week)	1.92 ± 0.49	25	1.83 ± 0.47	20	n.s.[a]
Average amount of plasma per session (L)	3.37 ± 0.57	23	3.67 ± 0.98	20	n.s.[a]
Duration of NS before the treatment <8 weeks	11 (48.8 %)	24	2 (5.3 %)	19	<0.05[b]
Male	14 (56.0 %)	25	14 (63.6 %)	22	n.s.[b]
Fatigue	17 (73.9 %)	23	13 (72.2 %)	18	n.s.[c]
Edema	23 (92.0 %)	25	16 (76.2 %)	21	n.s.[c]
First time	14 (56.0 %)	25	13 (61.9 %)	21	n.s.[b]
Renal biopsy	21 (84.0 %)	25	19 (86.4 %)	22	n.s.[c]
Cyclosporine A administration	12 (50.0 %)	24	12 (54.5 %)	22	n.s.[b]
Steroid pulse therapy	1 (4.2 %)	24	3 (13.6 %)	22	n.s.[c]

[a] Student's t test
[b] Chi-square test
[c] Fisher's exact test

respectively), and also UP at pre-treatment also showed lower trend in effective episodes ($p = 0.075$) (Tables 5, 6). Not to be argued, UP and SP are distinctive indicators for severity of NS. It is suggested that patient's clinical condition has an influence on efficacy of LDL-A treatment. Hattori et al. reported that a higher selectivity index and lower degree of tubular damage were observed in pediatric patients with steroid-resistant NS who responded to LDL-A treatment compared to those who did not respond. We evaluated the duration after onset of NS dichotomized by within or more than 8 weeks. As shown in Table 7, of 13 episodes in which LDL-A was applied within 8 weeks after the onset, 11 (84.6 %) were effectively treated and recovered from nephrotic condition, whereas efficacy of the other episodes was poor (13/30, 43.3 %). Taken together, it could be considered that the less serious glomerular dysfunction and/or renal tissue damage of patients, the more likely for them to achieve effective treatment. Therefore, we suggest that LDL-A should be used immediately when a patient with NS appears not to respond to primary medication to prevent progression of renal injury.

The results of the study showed the short-term clinical efficacy of LDL-A for the treatment of drug-resistant NS in the population of patients in the POLARIS study. However, several limitations in this study need to be addressed. Most importantly, this study was conducted in an observational manner and did not intervene with concomitant therapies including medications. Therefore, the contribution of the concomitant therapies was not elucidated. In addition, the study was a single-arm study without a control group and accordingly it was difficult to directly demonstrate the efficacy of the treatment. Furthermore, the sample size was rather small to make a convincing evaluation. Although the above-mentioned limitations should be taken into consideration, this study was performed prospectively in a nationwide multicenter cohort with many more NS episodes than in previous studies and demonstrated comparable efficacy to that in the previous studies. It will be intriguing to see whether the improved clinical conditions produced by LDL-A will continue for a longer period. The final results of the POLARIS study may reveal the long-term clinical efficacy of LDL-A as an alternative therapy for drug-resistant NS.

Table 7 Comparison of the therapeutic efficacy of LDL-A between patients who received treatment at less than ($n = 13$) and more than ($n = 30$) 8 weeks after onset of NS

Efficacy	Period before treatment	
	<8 weeks	≥8 weeks
Effective (*n*)	11	13
Non-effective (*n*)	2	17
Rate	84.6 %	43.3 %

The data for 4 episodes were not collected

Acknowledgments This study was supported by The Kidney Foundation, Japan and in part by a grant in relation to Progressive Renal Disease from the Ministry of Health, Labor and Welfare Research Project for Specially Selected Disease. The authors express their appreciation to all the investigators who reported clinical data in this study, including Atsushi Oyama (Nishi-Kobe Medical Center), Noriaki Henmi (Fukaya Red Cross Hospital), Noriko Mori (Shizuoka General Hospital), Osamu Nishi, (Nishi Clinic), Yasukiyo Mori (Kyoto Prefectural University of Medicine), Megumu Fukunaga (Toyonaka Municipal Hospital), Masahiko Miyamoto (Osaka Red Cross Hospital), Kenji Arizono (Kumamoto Chuo Hospital), Takako Suzuki (Moriyama Rehabilitation Hospital), Kazuhiko Hora (Hokushin General Hospital), Hiroshi Makino (Okayama University), Hideyasu Kiyomoto (Kagawa University), Yutaka Ando (Osaka Minami Medical Center), Yoshiharu Tsubakihara (Osaka General Medical Center), Kosuke Ota (Okayama Medical Center), Masamichi Fukuda (Iwakuni Medical Center Hospital), Yukiko Abe (Shin-Oura Hospital), Mitsuhiro Yoneda (Fuke Chiba Hospital), Hiroshi Ohtani (Akita Kumiai General Hospital), Tokuichiro Sugimoto (Mitsui Memorial Hospital), Shizunori Ichida (Japanese Red Cross Nagoya Daiichi Hospital), Kentaro Wada (Nippon Kokan Fukuyama

Hospital), Rhosuke Yoshihara (Konan Kakogawa Hospital), Shoichi Fujimoto (University of Miyazaki), Morihiro Kondo (Rakuwa-kai Otowa Hospital), Takeshi Nakanishi (Hyogo College of Medicine), Kazuhiko Tsuruya (Kyusyu University), Fumiki Tanigawa (Shimonoseki Kosei Hospital), Masami Hashimoto (Onomichi General Hospital), Akiko Nakamura (Saga Prefectural Hospital Koseikan), Soshi Yorifuji (Osaka Saiseikai Nakatsu Hospital), Tamaki Sasaki (Kawasaki Medical School).

Conflict of interest None of the authors report a conflict of interest with this study.

References

1. Moorhead JF, Chan MK, El-Nahas M, Varghese Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet. 1982;2:1309–11.
2. Buemi M, Nostro L, Crasci E, Barilla A, Cosentini V, Aloisi C, Sofi T, Campo S, Frisina N. Statins in nephrotic syndrome: a new weapon against tissue injury. Med Res Rev. 2005;25:587–609.
3. Ito S, Machida H, Inaba A, Harada T, Okuyama K, Nakamura T, Aihara Y, Yokota S. Amelioration of steroids and cyclosporine-resistant nephrotic syndrome by pravastatin. Pediatr Nephrol. 2007;22:603–6.
4. Yokoyama S, Hayashi R, Satani M, Yamamoto A. Selective removal of low density lipoprotein by plasmapheresis in familial hypercholesterolemia. Arteriosclerosis. 1985;5:613–22.
5. Tojo K, Sakai S, Miyahara T. Possible therapeutic application of low density lipoprotein apheresis (LDL-A) in conjunction with double filtration plasmapheresis (DFPP) in drug-resistant nephrotic syndrome due to focal glomerular sclerosis (FGS). Jpn J Nephrol. 1988;30:1153–60.
6. Hattori M, Chikamoto H, Akioka Y, Nakakura H, Ogino D, Matsunaga A, Fukazawa A, Miyakawa S, Khono M, Kawaguchi H, Ito K. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. Am J Kidney Dis. 2003;42:1121–30.
7. Yokoyama K, Sakai S, Sigematsu T, Takemoto F, Hara S, Yamada A, Kawaguchi Y, Hosoya T. LDL adsorption improves the response of focal glomerulosclerosis to corticosteroid therapy. Clin Nephrol. 1998;50:1–7.
8. Muso E, Yashiro M, Matsushima M, Yoshida H, Sawanishi K, Sasayama S. Does LDL-apheresis in steroid-resistant nephrotic syndrome affect prognosis? Nephrol Dial Transplant. 1994;9:257–64.
9. Muso E, Mune M, Fujii Y, Imai E, Ueda N, Hatta K, Imada A, Miki S, Kuwahara T, Takamitsu Y, Takemura T, Tsubakihara Y. Low density lipoprotein apheresis therapy for steroid-resistant nephrotic syndrome. Kansai-FGS-Apheresis Treatment (K-FLAT) Study Group. Kidney Int Suppl. 1999;71:S122–5.
10. Muso E, Mune M, Fujii Y, Imai E, Ueda N, Hatta K, Imada A, Takemura T, Miki S, Kuwahara T, Takamitsu Y, Tsubakihara Y. Significantly rapid relief from steroid-resistant nephrotic syndrome by LDL apheresis compared with steroid monotherapy. Nephron. 2001;89:408–15.
11. Muso E, Mune M, Yorioka N, Nishizawa Y, Hirano T, Hattori M, Sugiyama S, Watanabe T, Kimura K, Yokoyama H, Sato H, Saito T. Beneficial effect of low-density lipoprotein apheresis (LDL-A) on refractory nephrotic syndrome (NS) due to focal glomerulosclerosis (FGS). Clin Nephrol. 2007;67:341–4.
12. Kobayashi T, Ando Y, Umino T, Miyata Y, Muto S, Hironaka M, Asano Y, Kusano E. Complete remission of minimal-change nephrotic syndrome induced by apheresis monotherapy. Clin Nephrol. 2006;65:423–6.
13. Sato Y, Tsunoda S, Nozue T, Pan Q, Wakasugi H, Yoshimura A. Low-density lipoprotein apheresis therapy for steroid- and cyclosporine-resistant idiopathic membranous nephropathy. Intern Med. 2012;51:2597–602.
14. Schlondorff D. Cellular mechanisms of lipid injury in the glomerulus. Am J Kidney Dis. 1993;22:72–82.
15. Diamond JR, Pesek I, McCarter MD, Karnovsky MJ. Altered functional characteristics of rat macrophages during nephrosis. Synergistic effects of hypercholesterolemia. Am J Pathol. 1989;135:711–8.
16. Knisel W, Di Nicuolo A, Pfohl M, Muller H, Risler T, Eggstein M, Seifried E. Different effects of two methods of low-density lipoprotein apheresis on the coagulation and fibrinolytic systems. J Intern Med. 1993;234:479–87.
17. Tasaki H, Tsuda Y, Yamashita K, Toyokawa T, Yashiro A, Osajima A, Nakashima Y, Kuroiwa A. Removal of plasma fibrinogen by LDL apheresis. Jpn J Apheresis. 1997;16:263.
18. Petrichenko I, Daret D, Larrue J, Shakhov Y. Effect of VLDL on the inhibition of arachidonic acid transformation by dexamethasone in cultured smooth muscle cells. Biochim Biophys Acta. 1993;1166:183–7.
19. Leon C, Jia J, Qiu G, Hill JS, Wasan KM. Modification in low-density lipoprotein receptor expression affects cyclosporin A cellular uptake and cytotoxicity. J Pharm Sci. 2008;97:2350–61.
20. Ingulli E, Tejani A. Severe hypercholesterolemia inhibits cyclosporin A efficacy in a dose-dependent manner in children with nephrotic syndrome. J Am Soc Nephrol. 1992;3:254–9.
21. Stenvinkel P, Alvestrand A, Angelin B, Eriksson M. LDL-apheresis in patients with nephrotic syndrome: effects on serum albumin and urinary albumin excretion. Eur J Clin Invest. 2000;30:866–70.

V.　資料

爪膝蓋骨症候群 (ネイルパテラ症候群) および *LMX1B* 関連腎症

○ 概要

1, 概要

爪膝蓋骨症候群 (ネイルパテラ症候群) は爪形成不全、膝蓋骨の低形成あるいは無形成、腸骨の角状突起 (iliac horn)、肘関節の異形成を 4 主徴とする遺伝性疾患である。しばしば腎症を発症し、一部は末期腎不全に進行する。原因は *LMX1B* 遺伝子変異である。

爪、膝蓋骨、腸骨などの変化を伴わず、腎症だけを呈する nail-patella-like renal disease (NPLRD) や巣状分節性糸球体硬化症患者にも *LMX1B* 遺伝子変異を原因とする例が存在する。これら一連の疾患群は *LMX1B* 関連腎症と呼ばれる。

2, 原因

爪膝蓋骨症候群の原因は *LMX1B* の変異である。これまでに 130 種類以上の変異が同定されている。NPLRD の一部、また巣状分節性糸球体硬化症患者やステロイド抵抗性ネフローゼ症候群患者の一部からも *LMX1B* 変異が見いだされている。

病態発症メカニズムとしては *LMX1B* 変異による糸球体上皮細胞機能障害が推定される。

3、症状

(1) 爪膝蓋骨症候群 (ネイルパテラ症候群)

爪形成不全、膝蓋骨の低形成あるいは無形成、腸骨の角状突起 (iliac horn)、肘関節の異形成がみられるが、このうちの一つあるいは複数の症状のみを呈する場合が有る。約半数に腎症を合併する。症状としては無症候性の蛋白尿や血尿がみられる。特に高度の蛋白尿によりネフローゼ症候群を呈することがある。15%の症例で腎機能が進行性に悪化し末期腎不全に至る。

組織学的には光学顕微鏡レベルでは特異的な所見はないが、特徴的な所見としては電子顕微鏡所見では糸球体基底膜が不規則に肥厚し、またその緻密層に虫食い像 (moth-eaten appearance) や III 型コラーゲンの沈着を認める。

(2) *LMX1B* 関連腎症

腎外合併症はなく、腎症 (蛋白尿、血尿)、腎機能障害、腎不全を呈する。

爪膝蓋骨症候群の腎組織像と同様の電子顕微鏡所見を示す場合と、示さない場合が

報告されている。

4、治療法

爪膝蓋骨症候群における爪、膝、肘関節の異常に対しては効果的な治療法はない。

腎症に対しても特異的な治療は存在しない。しかし近年アンギオテンシン変換酵素阻害薬やアンギオテンシンII受容体拮抗薬などの腎不全予防治療が一定の効果を呈することが知られている。腎不全に至った場合には維持透析あるいは腎移植を要する。

5、予後

腎症が生命予後を規定する。3-5割に腎症を合併する。小児期に発症することも多い。そのうち1-3割で末期腎不全へと進行する。

○ 要件の判定に必要な事項

1. 患者数
   総患者数約500人程度と推計される
2. 発病の機構
   *LMX1B*遺伝子異常による
3. 効果的な治療方法
   未確立(対症療法のみである)
4. 長期の療養
   必要(腎不全に対する治療や腎代替療法が必要となる場合が有る)
5. 診断基準
   あり(日本腎臓学会と研究班が共同で作成した基準有り)
6. 重症度分類
   慢性腎臓病重症度分類で重症に該当するもの、あるいはいずれの腎機能であっても尿蛋白/クレアチニン比　0.5g/g・Cr以上のものを、重症として扱う。

○ 情報提供元

「*LMX1B*関連腎症の実態調査および診断基準の確立」研究班
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〈診断基準-爪膝蓋骨症候群〉

主項目を満たし、かつ副項目１項目以上を有し、さらに鑑別疾患を除外したものを爪膝蓋骨症候群と診断する。

主項目

爪の低形成あるいは異形成

（手指に多く、特に母指側に強い。程度は完全欠損から低形成まで様々である。三角状の爪半月のみを呈する場合もあり、軽症であると気づかれにくい。）

副項目

1. 膝蓋骨形成不全
2. 肘関節異常
3. 腸骨の角状突起
4. *LMX1B* 遺伝子のヘテロ接合体変異

参考項目

1. 爪膝蓋骨症候群の家族歴
2. 腎障害　（血尿、蛋白尿、あるいは腎機能障害）
3. 腎糸球体基底膜の特徴的電顕所見

   (腎障害が有った場合に腎生検を検討するが、本症の診断上は必須ではない。病理像としては腎糸球体基底膜の肥厚と虫食い像”moth-eaten appearance”が特徴的である。肥厚した糸球体基底膜中央の緻密層やメサンギウム基質内に III 型コラーゲン繊維の沈着が見られる。これらの線維成分はリンタングステン酸染色あるいはタンニン酸染色で染色される)

鑑別診断

1. Meier-Gorlin 症候群 (OMIM224690),
2. Genitopatellar 症候群 (OMIM606170)
3. DOOR 症候群 (OMIM220500)
4. ８トリソミーモザイク症候群
5. Coffin-Siris 症候群 (OMIM135900) / BOD 症候群 (OMIM113477)
6. RAPADILINO 症候群 (OMIM266280)

〈診断基準-*LMX1B*関連腎症〉

主項目の三つを満たし、副項目の少なくとも一つを満たすものを*LMX1B*関連腎症と診断する。

主項目

1. 腎障害　（血尿、蛋白尿、あるいは腎機能障害）
2. 爪膝蓋骨症候群の診断基準を満たさない
3. 腎障害を来す他の原因(遺伝子異常など)を有さない

副項目

1. *LMX1B*遺伝子のヘテロ接合体変異
2. 腎糸球体基底膜の特徴的電顕所見

(腎生検病理において、腎糸球体基底膜の肥厚と虫食い像”moth-eaten appearance”を認め、さらにリンタングステン酸染色あるいはタンニン酸染色により基底膜内に線維成分が染色される)

注.　尿所見異常あるいは腎機能障害あり、腎生検所見で腎糸球体基底膜の特徴的電顕所見が有った場合あるいは常染色体優性遺伝形式を示す家族歴を有する場合に*LMX1B*遺伝子検査を考慮する。

〈重症度分類　（爪膝蓋骨症候群および *LMX1B* 関連腎症共通）〉

慢性腎臓病重症度分類で重症に該当するもの（下図赤）、あるいはいずれの腎機能であっても尿蛋白／クレアチニン比　0.5g/g・Cr 以上のものを、重症として扱う。

原疾患		蛋白尿区分		A1	A2	A3
糖尿病		尿アルブミン定量（mg/日） 尿アルブミン/Cr 比（mg/gCr）		正常	微量アルブミン尿	顕性アルブミン尿
				30 未満	30～299	300 以上
高血圧 腎炎 多発性嚢胞腎 移植腎 不明 その他		尿蛋白定量（g/日） 尿蛋白/Cr 比（g/gCr）		正常	軽度蛋白尿	高度蛋白尿
				0.15 未満	0.15～0.49	0.50 以上
GFR区分（mL/分/1.73 m²）	G1	正常または高値	≧90			
	G2	正常または軽度低下	60～89			
	G3a	軽度～中等度低下	45～59			
	G3b	中等度～高度低下	30～44			
	G4	高度低下	15～29			
	G5	末期腎不全（ESKD）	＜15			

重症度は原疾患・GFR 区分・蛋白尿区分を合わせたステージにより評価する．CKD の重症度は死亡，末期腎不全，心血管死亡発症のリスクを緑のステージを基準に，黄，オレンジ，赤の順にステージが上昇するほどリスクは上昇する．（KDIGO CKD guideline 2012 を日本人用に改変）

※なお、症状の程度が上記の重症度分類等で一定以上に該当しないが、高額な医療を継続することが必要な者については、医療費助成の対象とする。