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Article

The Long-Term Effects of the Selective Inhibitor of Urate Transporter 1, Dotinurad, on Metabolic Parameters and Renal Function in Patients with Asymptomatic Hyperuricemia

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Abstract: Background/Objectives: A great number of epidemiological studies have reported that hyperuricemia is associated with the development of hypertension, dyslipidemia, type 2 diabetes, chronic kidney disease (CKD), in addition to metabolic syndrome and insulin resistance. We investigated the effects of long-term treatment with the novel uricosuric drug, a highly selective inhibitor of urate transporter 1 (URAT1), on metabolic parameters and renal function. Methods: We retrospectively picked up patients who had taken dotinurad for the treatment of asymptomatic hyperuricemia, for more than 2 years. We compared metabolic parameters and renal function at baseline with the data at 6, 12, 18, and 24 months after the start of dotinurad. Results: Pharmacologically, dotinurad decreases serum uric acid (UA), by selectively inhibiting URAT1 and decreasing renal reabsorption of UA, which was supported by our result that dotinurad significantly increased urine UA and reduced serum UA. In addition to UA-lowering, dotinurad significantly improved body weight, liver function, serum lipids, and urine albumin. The ATP-binding cassette transporter G2 (ABCG2) regulates renal and intestinal excretion of UA and uremic toxins and strongly affects renal function. Our study also indicates that switching from febuxostat, which inhibits ABCG2, to dotinurad, which does not inhibit ABCG2, was beneficial for maintaining the GFR. Conclusions: Dotinurad may improve obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and CKD by blocking the entry of UA via URAT1 to adipose tissue, liver, and kidney.

Keywords: ATP-binding cassette transporter G2; chronic kidney disease; dotinurad; metabolic dysfunction-associated steatotic liver disease; urate transporter 1

1. Introduction

An excess serum uric acid (UA) level, even within the normal range, is always comorbid with metabolic syndrome, several of its components. The meta-analysis using 11 studies (54970 participants and 8719 metabolic syndrome cases) suggested that higher serum UA levels led to an increased risk of metabolic syndrome regardless of the study characteristics, and were consistent with a linear dose-response relationship [1]. This study also showed that each 1 mg/dl serum UA level increment led to 21% increase in the metabolic dysfunction-associated steatotic liver disease (MASLD) risk (relative risk [RR], 1.21; 95% confidence interval [CI], 1.03 to 1.41). Serum UA levels increased with the number of components of metabolic syndrome adjusted for age, sex, creatinine clearance, and alcohol, and diuretic use [2]. Visceral fat area was the most important determinant of elevation in serum UA and a reduced UA clearance [3]. Insulin resistance was significantly and inversely related to urine UA clearance [4].

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A great number of epidemiological studies have suggested that hyperuricemia is associated with the development of hypertension, dyslipidemia, type 2 diabetes, chronic kidney disease (CKD) and chronic kidney disease (CVD), in addition to metabolic syndrome and insulin resistance **[5–9]**. Recent studies suggest that serum UA may have a variety of pro-inflammatory, pro-oxidative and vasoconstrictive actions that may contribute to cardiometabolic diseases [9]. The meta-analysis showed that almost 20% of patients with hyperuricemia have diabetes [10]. A national cohort study and updated meta-analysis showed that participants in the highest serum UA quartile were 2.73 times as likely to develop incident CKD compared to those in the lowest quartile (odds ratio [OR], 2.73; 95% CI, 1.65 to 4.50) and each 1 mg/dl increment in the serum UA levels was associated with a 49% increased risk of incident CKD [11]. In another meta-analysis, hyperuricemia was significantly associated with an increased risk of new-onset CKD (RR, 1.71; 95% CI, 1.56 to 1.87) [12].

Xanthine oxidase (XO) inhibitors, allopurinol, and febuxostat treatments induced a significant reduction in body weight, systolic blood pressure, blood glucose, insulin, and lipids, and improved kidney and endothelial function compared to nontreated metabolic syndrome model rats [13]. To understand the effect of UA-lowering therapy on serum lipids, a retrospective study using 124 gouty patients with hypercholesterolemia or hypertriglyceridemia was performed [14]. Fifty-two were treated with febuxostat, 29 were treated with allopurinol, and 43 were treated with the uricosuric drug benzbromarone, which inhibits both urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9), which reabsorbs UA in the kidneys. All therapies mildly influenced serum cholesterol and triglyceride (TG) levels, and febuxostat significantly decreased cholesterol and TG levels in patients who did not receive lipid-lowering therapy. Allopurinol and benzbromarone modestly decreased TG levels, but did not influence serum cholesterol levels. Very recently, a sub-analysis of the PRIZE study in which the effects of febuxostat on carotid atherosclerosis in patients with hyperuricemia was reported [15]. Serum non-HDL-C levels were significantly reduced in the febuxostat group (-5.9 mg/dl; 95% CI, -9.1 to -2.8 mg/dL; $p < 0.001$), but not in the control group (-1.3 mg/dL; 95% CI, -4.4 to 1.8; $p = 0.348$) after the start of febuxostat.

Allopurinol ameliorated high fructose diet-induced hepatic steatosis through modulation of hepatic lipid metabolism, inflammation, and endoplasmic reticulum (ER) stress pathway in rats, suggesting that UA may have a direct role in the development of fructose-induced hepatic steatosis, and allopurinol could be a candidate for prevention or treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) [16]. Recently, a study evaluated the effects of allopurinol 100 mg or febuxostat 40 mg daily plus lifestyle modifications compared to lifestyle modifications alone on improving steatosis was performed [17]. The controlled attenuation parameter (CAP) score as an indicator of steatosis decreased significantly in the allopurinol group ($p = 0.009$), but the decline in the febuxostat or lifestyle groups was non-significant ($p = 0.189$ and 0.054, respectively).

In the meta-analysis of 4 randomized clinical trials (RCTs) comparing the efficacy and -safety of allopurinol in patients with CKD, allopurinol significantly increased the estimated glomerular filtration rate (eGFR) compared with control groups (standard mean difference [SMD], 2.04; 95% CI, 0.60 to 3.49; $p = 0.005$) [18]. Another meta-analysis showed that febuxostat presented a reno-protective effect in CKD patients [19]. However, very recently, the Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) Study Group reported that UA-lowering therapy was not associated with slowing CKD progression [20].

Different effects of each UA-lowering drug on metabolic parameters such as MASLD and dyslipidemia have been reported. Furthermore, there is a controversial discussion on the influence of UA-lowering drugs on the onset and progression of CKD. The novel uricosuric drug, a highly selective inhibitor of urate transporter 1 (URAT1), dotinurad, was developed and is available in Japan [21]. Here, we investigated the effects of long-term treatment with dotinurad on metabolic parameters and renal function.

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2. Materials and Methods

2.1. Study Population

The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-S-004957-00), and the study was performed in accordance with the Declaration of Helsinki.

We retrospectively picked up patients who had taken dotinurad for the treatment of asymptomatic hyperuricemia, for more than 2 years. These patients had been regularly attending the Department of General Internal Medicine or the Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine Kohnodai Hospital, Japan. We compared metabolic parameters and renal function at baseline with the data at 6, 12, 18 and 24 months after the start of dotinurad. Age, gender, body weight, body mass index (BMI), systolic and diastolic blood pressures, comorbidities were obtained via an electronic medical record. Informed consent was obtained by the opt-out approach. Hyperuricemia was diagnosed by taking UA-lowering drugs and/or serum UA ≥ 7.0 mg/dL, respectively.

2.2. Laboratory Measurements

Body weight, height, and blood pressure were measured according to the clinical standards. Body mass index (BMI) was calculated by dividing body weight in kilograms by body height squared in meters. The measurements of hemoglobin A1c (HbA1c), total cholesterol (TC), and TG were performed using enzymatic assays. Serum and urine UA were measured using the uricase-peroxidase method. A direct method was used to measure serum low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C). Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (GGT) were measured by using the Japan Society of Clinical Chemistry transferable method. The estimated glomerular filtration rate (eGFR) was calculated by age and serum creatinine, measured by the enzymatic assay based on the estimation equation for Japanese patients [22]. Non-HDL-C was calculated by subtracting HDL-C from TC. Urinary albumin levels were measured by the turbidimetric immunoassay. Urinary excretion of albumin and UA were evaluated by dividing by urine creatinine such as urine albumin-creatinine ratio (UACR) and urine UA/creatinine. Since eGFR varies widely between patients, eGFR slope was evaluated by setting the baseline data of each patient as 100% and evaluating the change in eGFR as percent changes at each observation period. This analytical method was also used to analyze the correlation between changes in eGFR with changes in serum and urinary UA levels.

2.3. Statistical Analysis

Comparisons between baseline data and the data after the start of dotinurad were analyzed by the paired t-tests. Spearman's rank correlation coefficient was used to determine the correlations between the parameters. Missing data were excluded from analyses. All data are expressed as mean ± SD, and $p < 0.05$ was considered statistically significant. We used SPSS version 29 (IBM Corp, Armonk, NY, USA) for statistical analysis.

3. Results

3.1. Characteristics of Patients Studied

3.1.1. Clinical and Laboratory Characteristics of Patients Studied at Baseline

During the observation period, 73 patients had taken dotinurad for 2 years. The clinical and laboratory characteristics of the patients studied are shown in Table 1. The mean BMI was 28.3 kg/m^{2,} and more than 60% of patients had a BMI of 25 or more. Over 60% of patients had type 2 diabetes and dyslipidemia, and over half of patients had hypertension. Serum UA levels were within normal range because patients already treated with other UA-lowering drugs were included. The mean

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values of AST and ALT were within normal range. The mean value of GGT was close to the upper limit of normal range in males and was above the normal range in females. The mean values of TG and HbA1c were above the upper limit of normal range. The mean value of eGFR was within normal range.

Table 1. Clinical and laboratory characteristics of patients studied at baseline (n = 73).

Clinical characteristics		
Gender (male/female)	50/23	
Age (years)	66.1±14.6	
Body height (cm)	162.7±19.9	
Body weight (kg)	76.7±17.4	
Body mass index (kg/m^2)	28.3±5.5	
Patients with body mass index ≧ 25 kg/m^2 (n, %)	48, 65.8%	
Systolic blood pressure (mmHg)	133.8±20.1	
Diastolic blood pressure (mmHg)	76.6±12.4	
Comorbidities		
Type 2 diabetes	48, 65.8%	
Hypertension	40, 54.8%	
Dyslipidemia	44, 60.3%	
Laboratory characteristics		
	Data at baseline	Normal range
Serum UA (mg/dl)	6.8±1.6	< 7
AST (IU/l)	25.9±9.7	13-30
ALT (IU/l)	28.2±19.6	Male 10-42 Female 7-23
GGT (IU/l)	50.6±49.0	Male 13-64 Female 9-32
HDL-C (mg/dl)	53.7±15.6	< 40
LDL-C (mg/dl)	100.1±26.8	< 140
TG (mg/dl)	182.6±126.2	Non-fasting value < 175
Non-HDL-C (mg/dl)	130.9±29.7	< 170
HbA1c (%)	6.7±1.6	4.9-6.0
eGFR (ml/min/1.73m^2)	61.2±20.4	60 <

Presented values indicate mean±SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride; UA, uric acid.

3.1.2. The Daily Doses of Dotinurad Used in Patients Studied

The daily doses of dotinurad used in patients are shown in Table 2. The daily doses of dotinurad were most commonly used in the order of 1.0 mg, 0.5 mg, and 2.0 mg, with only two patients using up to 4.0 mg.

Table 2. The daily doses of dotinurad used in patients studied.

Daily doses of dotinurad	n (%)
0.5 mg	23 (31.5%)
1.0 mg	28 (38.4%)
2.0 mg	20 (27.4%)
4.0 mg	2 (2.7%)

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3.1.2. The UA-Lowering Drugs Used in Patients Studied Before the Start of Dotinurad

The UA-lowering drugs that patients had taken before the start of dotinurad are shown in Table 3. Fifty-two percent of patients had no prior treatment for hyperuricemia and were initiated on dotinurad for the first time. Before switching to dotinurad, all patients whose hyperuricemia was already treated had taken oral xanthine oxidase (XO) inhibitors. Three kinds of XO inhibitors were used. Febuxostat was frequently used.

Table 3. The UA-lowering drugs used in patients before the start of dotinurad.

Kind of UA-lowering drugs	n (%)
Febuxostat	26 (36%)
Topiroxostat	3 (4%)
Allopurinol	6 (8%)
No drugs	38 (52%)

3.2. Changes in Metabolic Parameters and Renal Function by the 2-Year-Dotinurad Treatment

3.2.1. Changes in Metabolic Parameters and Renal Function at 6, 12, 18 and 24 Months After the Start of Dotinurad in All Patients

Changes in metabolic parameters at 6, 12, 18, and 24 months after the start of dotinurad in all patients were shown in Table 4. Dotinurad significantly decreased serum UA levels and increased urine UA levels at 6, 12, 18, and 24 months. Body weight significantly decreased at 6 and 24 months after the start of dotinurad. Systolic blood pressure significantly decreased after 2 years. Serum ALT and GGT levels significantly decreased after 12 and 24 months. Serum HDL-C significantly increased at 6 months after the start of dotinurad, and non-HDL-C significantly decreased after 6, 12, 18, and 24 months. The eGFR significantly decreased after 12, 18 and 24 months. Urine albumin significantly decreased at 6 months after the start of dotinurad.

Table 4. Changes in metabolic parameters at 6, 12, 18 and 24 months after the start of dotinurad in all patients.

	N	Baseline	After 6 m.	N	Baseline	After 12 m.	N	Baseline	After 18 m.	N	Baseline	After 24 m.
Body weight (kg)	67	76.6±17.0	75.6±16.4*	66	76.2±17.2	75.7±17.3	67	76.7±17.6	76.3±18.1	66	76.7±17.7	75.4±18.0*
Systolic BP (mmHg)	69	133.1±19.5	133.1±14.7	68	132.9±19.6	131.6±16.2	67	132.4±19.0	130.8±13.8	67	133.2±19.9	128.4±14.1*
Diastolic BP (mmHg)	69	76.5±12.4	77.4±11.7	68	76.2±12.3	74.4±12.5	67	76.3±12.5	76.3±13.0	67	76.3±12.5	73.9±13.1
Serum UA (mg/dl)	72	6.7±1.6	5.8±1.2*	73	6.8±1.6	5.7±1.0*	73	6.8±1.6	5.5±1.3*	71	6.7±1.6	6.7±5.5*
Urine UA (/creatinine)	47	0.34±0.16	0.46±0.25*	49	0.35±0.17	0.44±0.24*	47	0.36±0.17	0.45±0.12*	46	0.35±0.17	0.52±0.23*
HbA1c (%)	67	6.7±1.1	6.7±0.9	69	6.7±1.1	6.7±0.9	69	6.7±1.1	6.7±0.9	66	6.7±1.1	6.7±0.9
AST (IU/l)	72	26.0±9.8	24.8±10.0	73	25.9±9.7	25.1±9.7	73	25.9±9.7	26.4±14.1	73	25.5±9.0	25.0±8.2
ALT (IU/l)	72	28.4±19.7	26.2±19.7	73	28.2±19.6	25.5±15.7*	73	28.2±19.6	27.3±22.4	71	27.9±19.8	24.7±13.4*
GGT (IU/l)	67	50.9±49.6	49.6±60.8	69	50.6±49.0	43.7±48.1*	69	50.6±49.0	44.4±56.2	67	48.4±46.9	39.4±29.5*
TG (mg/dl)	72	181.6±126.8	159.2±90.1	73	182.6±126.2	164.8±105.6	73	182.6±126.2	164.0±97.0	73	182.2±128.8	162.9±129.5
HDL-C (mg/dl)	72	53.9±15.7	56.6±15.7*	73	53.7±15.6	53.3±15.7	73	53.7±15.6	54.4±15.5	70	53.2±15.1	53.0±14.0
LDL-C (mg/dl)	65	99.9±26.7	100.8±25.5	65	99.9±26.7	96.8±23.3	66	100.5±26.9	96.8±26.6	63	100.7±26.3	95.9±25.2
Non-HDL-C (mg/dl)	63	130.5±29.5	124.1±28.2*	63	131.2±30.3	120.9±25.2*	63	131.2±30.3	120.3±25.7*	61	132.3±30.1	121.8±26.4*
eGFR (ml/min/1.73m^2)	72	61.8±20.0	60.4±20.2	73	61.2±20.4	59.2±19.6*	73	61.2±20.4	58.1±18.4*	71	60.7±20.1	57.4±20.2*
UACR (/creatinine)	42	240.1±444.7	134.0±335.1*	45	309.3±541.6	334.5±672.9	44	270.3±477.2	204.7±395.4	40	278.4±492.3	180.3±435.0

Presented values indicate mean±SD. *p < 0.05 vs. baseline values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride; UACR, urine albumin-creatinine ratio.

3.2.2. Changes in Metabolic Parameters at 6, 12, 18, and 24 Months After the Start of Dotinurad in Patients Naïve to UA-Lowering Drugs

Changes in metabolic parameters at 6, 12, 18, and 24 months after the start of dotinurad in patients naïve to UA-lowering drugs were shown in Table 5. Dotinurad significantly decreased serum UA levels at 6, 12, 18, and 24 months. Serum LDL-C significantly decreased at 12, 18, and 24

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months after the start of dotinurad, and non-HDL-C significantly decreased after 6, 12, 18, and 24 months. The eGFR significantly decreased after 6, 18 and 24 months. Urine albumin significantly decreased at 6 and 24 months after the start of dotinurad.

Table 5. Changes in metabolic parameters at 6, 12, 18, and 24 months after the start of dotinurad in patients naïve to UA-lowering drugs.

	N	Baseline	After 6 m.	N	Baseline	After 12 m.	N	Baseline	After 18 m.	N	Baseline	After 24 m.
Body weight (kg)	35	71.9±17.0	71.1±16.2	35	71.6±17.3	71.2±17.1	35	71.6±17.3	71.3±17.6	33	70.9±17.5	69.5±17.6
Systolic BP (mmHg)	36	133.3±20.2	133.9±15.0	36	133.4±20.4	131.8±16.4	35	132.1±19.1	130.5±14.5	34	133.5±21.0	127.9±12.9
Diastolic BP (mmHg)	36	75.9±13.6	77.4±11.4	36	75.6±13.5	73.4±12.8	35	75.5±13.6	76.5±12.3	34	75.5±13.8	72.3±11.1
Serum UA (mg/dl)	37	7.7±1.4	5.8±1.1*	38	7.7±1.4	5.8±0.9*	38	7.7±1.4	5.5±1.2*	36	7.7±1.4	5.6±1.5*
Urine UA (/creatinine)	20	0.41±0.18	0.45±0.23	22	0.43±0.19	0.42±0.22	22	0.43±0.19	0.42±0.21	20	0.44±0.20	0.52±0.23
HbA1c (%)	35	6.8±1.2	6.8±0.9	36	6.8±1.2	6.7±0.8	36	6.8±1.2	6.8±0.9	34	6.9±1.2	6.9±0.8
AST (IU/l)	37	25.2±8.6	24.6±8.1	38	25.0±8.5	23.9±7.8	38	25.0±8.5	25.1±12.6	36	24.2±6.6	24.1±7.2
ALT (IU/l)	37	25.7±16.7	22.9±11.4	38	25.5±16.5	22.3±11.8	38	25.5±16.5	24.1±15.2	36	24.8±16.7	22.4±12.0
GGT (IU/l)	37	45.0±36.8	41.4±31.4	38	44.6±36.3	38.9±38.1	38	44.6±36.3	35.4±22.3	36	40.3±28.6	34.7±19.1
TG (mg/dl)	37	192.2±157.3	162.2±96.7	38	194.0±155.5	174.0±126.1	38	194.0±155.5	166.4±92.6	36	193.4±160.0	180.6±157.0
HDL-C (mg/dl)	37	51.3±15.8	54.9±17.0	38	51.1±15.6	48.6±12.0	38	51.1±15.6	51.5±13.0	36	50.8±15.1	48.8±12.9
LDL-C (mg/dl)	37	105.1±32.0	101.5±24.0	38	105.9±32.0	96.7±21.7*	38	105.9±32.0	96.4±26.1*	36	105.6±31.7	96.4±28.3*
Non-HDL-C (mg/dl)	37	122.6±39.4	112.0±37.0*	38	124.3±40.2	108.6±34.9*	38	124.3±40.2	107.6±34.0*	36	127.1±38.4	113.1±32.4*
eGFR (ml/min/1.73m²)	37	58.6±17.9	55.8±14.1*	38	57.6±18.6	55.0±16.0	38	57.6±18.6	53.9±14.5*	36	56.4±17.5	51.4±14.7*
UACR (/creatinine)	21	276.1±471.7	181.3±435.5*	26	323.7±584.1	338.1±649.2	24	269.2±484.2	195.0±397.0	23	252.9±486.7	125.9±256.8*

Presented values indicate mean±SD. *p < 0.05 vs. baseline values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride; UACR, urine albumin-creatinine ratio.

3.2.3. Changes in Metabolic Parameters at 6, 12, 18, and 24 Months After the Start of Dotinurad in Patients Who Switched from XO Inhibitors

Changes in metabolic parameters at 6, 12, 18, and 24 months after the start of dotinurad in patients who switched from XO inhibitors were shown in Table 6. Although dotinurad did not change serum UA levels, urine UA significantly increased at 6, 12, 18, and 24 months. Body weight significantly decreased after 6 months. HbA1c significantly increased after 12 months. Serum GGT significantly decreased after 12 and 24 months.

Table 6. Changes in metabolic parameters at 6, 12, 18, and 24 months after the start of dotinurad in patients who switched from XO inhibitors.

	N	Baseline	After 6 m.	N	Baseline	After 12 m.	N	Baseline	After 18 m.	N	Baseline	After 24 m.
Body weight (kg)	32	81.7±15.8	80.6±15.2*	31	81.3±16.0	80.8±16.3	32	82.4±16.3	82.0±17.2	33	82.4±16.1	81.3±16.6
Systolic BP (mmHg)	33	133.0±19.0	132.2±14.6	32	132.4±19.0	131.3±16.2	33	132.6±19.2	131.2±13.3	33	132.9±19.0	128.9±15.5
Diastolic BP (mmHg)	33	77.2±11.2	77.5±12.2	32	76.8±11.1	75.5±12.2	33	77.3±11.3	76.1±14.0	33	77.2±11.2	75.5±14.8
Serum UA (mg/dl)	35	5.8±1.2	5.8±1.3	35	5.8±1.2	5.7±1.2	35	5.8±1.2	5.6±1.4	35	5.8±1.2	5.5±1.3
Urine UA (/creatinine)	27	0.29±0.12	0.46±0.27*	27	0.29±0.12	0.47±0.26*	25	0.29±0.12	0.48±0.19*	26	0.29±0.12	0.53±0.23*
HbA1c (%)	32	6.5±0.9	6.6±1.0	33	6.5±0.9	6.7±1.0*	33	6.5±0.9	6.6±1.0	32	6.5±1.0	6.6±0.9
AST (IU/l)	35	26.8±10.9	25.1±11.8	35	26.8±10.9	26.4±11.5	35	26.8±10.9	27.8±15.6	35	26.8±10.9	26.0±9.2
ALT (IU/l)	35	31.1±22.3	29.6±25.6	35	31.1±22.3	29.0±18.7	35	31.1±22.3	30.8±28.1	35	31.1±22.3	27.0±14.5
GGT (IU/l)	30	58.2±61.9	59.8±83.6	31	57.9±60.9	49.6±58.1*	31	57.9±60.9	55.6±79.5	31	57.9±60.9	44.9±38.0*
TG (mg/dl)	35	170.3±84.2	155.9±83.8	35	170.4±84.2	154.8±78.1	35	170.3±84.2	161.4±103.1	34	170.4±85.5	144.1±90.6
HDL-C (mg/dl)	35	56.6±15.3	58.3±14.2	35	56.6±15.3	58.5±17.8	35	56.6±15.3	57.6±17.5	34	55.8±14.8	57.2±14.1
LDL-C (mg/dl)	33	99.6±27.3	102.2±27.1	33	99.6±27.3	99.2±26.4	33	99.6±27.3	97.3±27.3	32	100.7±27.0	97.7±25.0
Non-HDL-C (mg/dl)	32	128.5±27.8	125.2±27.8	32	128.5±27.8	120.5±26.4	32	128.5±27.8	121.7±25.5	31	129.8±27.1	121.4±27.3
eGFR (ml/min/1.73m²)	35	65.1±21.8	65.3±24.2	35	65.1±21.8	63.7±22.2	35	65.1±21.8	62.6±21.1	35	65.1±21.8	63.5±23.4

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UACR (/creatinine)	21	204.1±424.5	86.7±189.4	19	282.7±491.9	329.6±722.0	20	271.6±481.3	216.3±403.7	17	312.9±512.8	253.9±600.4

Presented values indicate mean±SD. *p < 0.05 vs. baseline values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride; UACR, urine albumin-creatinine ratio.

3.2.4. Changes in Metabolic Parameters at 6, 12, 18 and 24 Months After the Start of Dotinurad in Patients Who Switched from Febuxostat

Changes in metabolic parameters at 6, 12, 18 and 24 months after the start of dotinurad in patients who switched from febuxostat were shown in Table 7. Although dotinurad did not change serum UA levels, urine UA significantly increased at 6, 12, 18, and 24 months. Serum ALT significantly decreased after 24 months, and serum GGT significantly decreased after 12 and 24 months. Serum TG significantly decreased after 24 months, and non-HDL-C significantly decreased after 12 months.

Table 7. Changes in metabolic parameters at 6, 12, 18 and 24 months after the start of dotinurad in patients who switched from febuxostat.

	N	Baseline	After 6 m.	N	Baseline	After 12 m.	N	Baseline	After 18 m.	N	Baseline	After 24 m.
Body weight (kg)	23	82.9±15.7	81.5±15.1	22	82.4±15.9	81.1±16.4	23	83.8±16.4	82.8±17.3	24	83.8±16.0	82.1±17.0
Systolic BP (mmHg)	25	131.3±19.5	129.6±10.7	24	130.5±19.5	129.0±16.1	24	130.8±19.8	129.9±13.9	25	131.3±19.5	126.1±15.6
Diastolic BP (mmHg)	25	76.1±11.8	75.6±11.0	24	75.5±11.7	72.9±11.0	24	76.2±12.1	75.1±13.8	25	76.1±11.8	73.8±15.4
HbA1c (%)	23	6.3±0.9	6.4±0.9	24	6.3±0.9	6.5±0.9	24	6.3±0.9	6.5±1.0	24	6.3±0.9	6.5±0.8
AST (IU/l)	26	28.2±12.1	26.7±13.2	26	28.2±12.1	27.6±12.9	26	28.2±12.1	29.0±17.6	26	28.2±12.2	26.4±9.7
Serum UA (mg/dl)	26	5.5±1.0	5.6±1.3	26	5.5±1.0	5.6±1.1	26	5.5±1.0	5.2±1.4	26	5.5±1.0	5.4±1.0
Urine UA (/creatinine)	23	0.27±0.11	0.46±0.27*	23	0.27±0.11	0.48±0.27*	21	0.27±0.12	0.48±0.20*	22	0.27±0.12	0.55±0.22*
ALT (IU/l)	26	34.1±24.8	32.2±28.8	26	34.1±24.8	30.7±20.9	26	34.1±24.8	32.6±32.1	26	34.1±24.8	28.1±15.5*
GGT (IU/l)	22	56.5±60.5	52.1±68.1	23	56.1±59.2	48.3±59.6*	23	56.1±59.2	45.8±41.2	23	56.1±59.2	44.1±36.4*
TG (mg/dl)	26	170.1±84.9	143.1±64.1	26	170.1±84.9	145.6±72.0	26	170.1±84.9	146.9±84.0	26	170.1±84.9	132.8±67.8*
HDL-C (mg/dl)	26	55.5±13.7	57.9±13.6	26	55.5±13.7	58.3±18.5	26	55.5±13.7	57.5±18.0	26	55.5±13.7	57.2±13.9
LDL-C (mg/dl)	25	96.6±21.0	98.6±26.9	25	96.6±21.0	96.7±24.7	25	96.6±21.0	95.9±27.0	25	96.6±21.0	95.0±25.1
Non-HDL-C (mg/dl)	23	124.9±24.2	119.6±27.2	23	124.9±24.2	114.8±23.1*	23	124.9±24.2	116.0±22.6	23	124.9±24.2	116.6±26.6
eGFR (ml/min/1.73m^2)	26	64.4±19.8	63.8±19.7	26	64.4±19.8	63.0±18.6	26	64.4±19.8	62.0±18.3	26	64.4±19.8	62.0±18.9
UACR (/creatinine)	15	200.1±452.2	58.4±84.6	12	242.1±500.6	201.2±322.1	13	228.1±481.9	153.4±195.5	11	260.9±520.6	98.6±105.1

Presented values indicate mean±SD. *p < 0.05 vs. baseline values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride; UACR, urine albumin-creatinine ratio.

3.3. Correlations of Serum and Urine UA Levels with eGFR at Baseline and 24 Months After the Start of Dotinurad

3.3.1. Correlations Between Serum UA Levels and eGFR at Baseline and 24 Months After the Start of Dotinurad

Correlations between serum UA levels and eGFR at baseline and 24 months after the start of dotinurad are shown in Figure 1. Serum UA levels were not significantly correlated with eGFR at both baseline and 24 months after the start of dotinurad.

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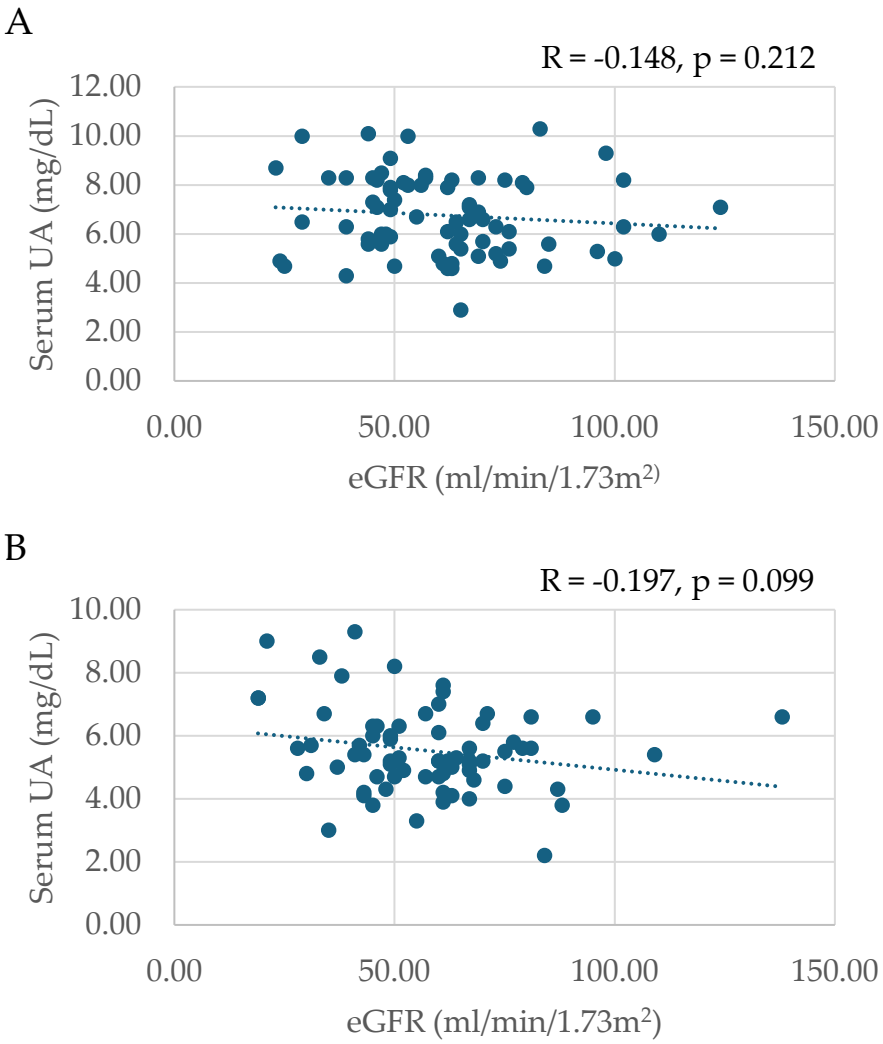

Figure 1. Correlations between serum UA levels and eGFR at baseline (A) and 24 months after the start of dotinurad (B).

3.3.2. Correlations Between Urine UA Levels and eGFR at Baseline and 24 Months After the Start of Dotinurad

Correlations between urine UA levels and eGFR at baseline and 24 months after the start of dotinurad are shown in Figure 2. Urine UA levels were not significantly correlated with eGFR at baseline. However, urine UA levels were significantly and positively correlated with eGFR at 24 months after the start of dotinurad.

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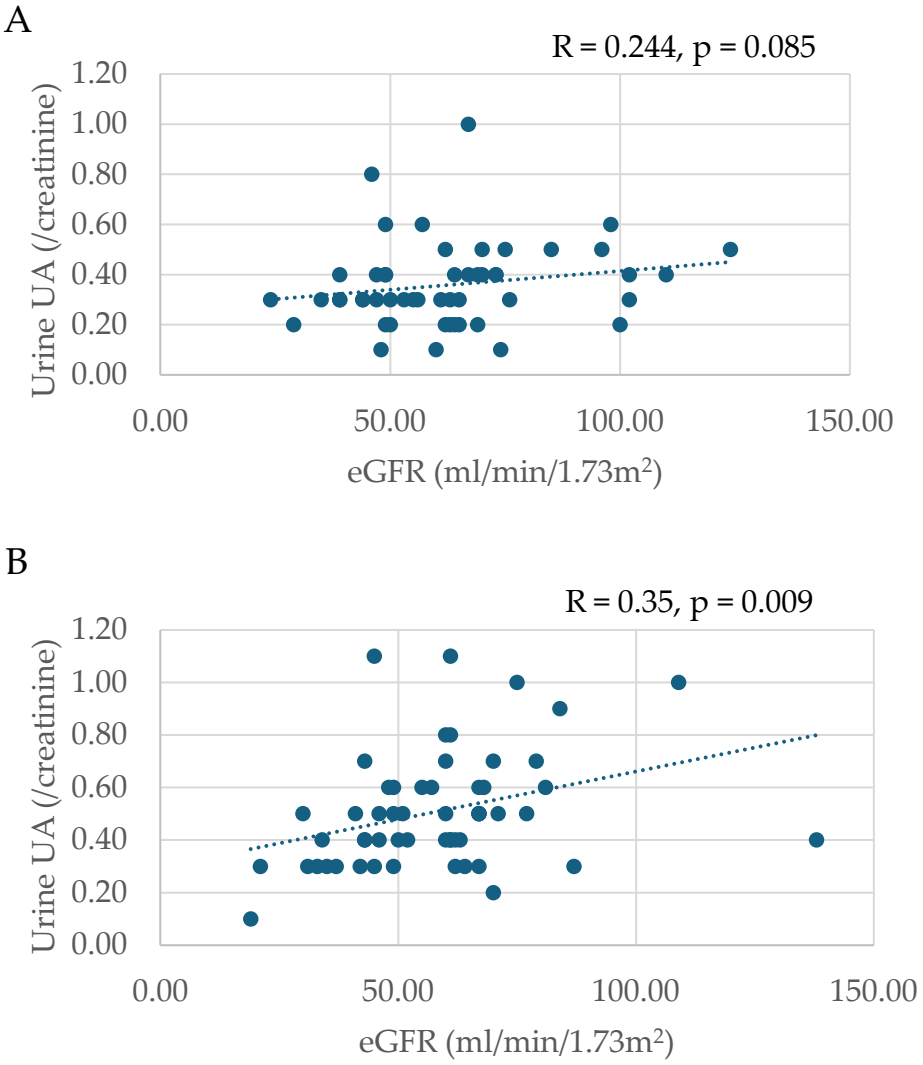

Figure 2. Correlations between urine UA levels and eGFR at baseline (A) and 24 months after the start of dotinurad (B).

3.3.3. Correlations of % Change in eGFR After 24 Months from Baseline with % Changes in Serum and Urine UA Levels After 24 Months from Baseline

Correlation of % change in eGFR after 24 months from baseline with % changes in serum and urine UA levels after 24 months from baseline are shown in Figure 3. The % change in serum UA was significantly and negatively correlated with the % change in eGFR. The % change in urine UA was significantly and negatively correlated with the % change in eGFR.

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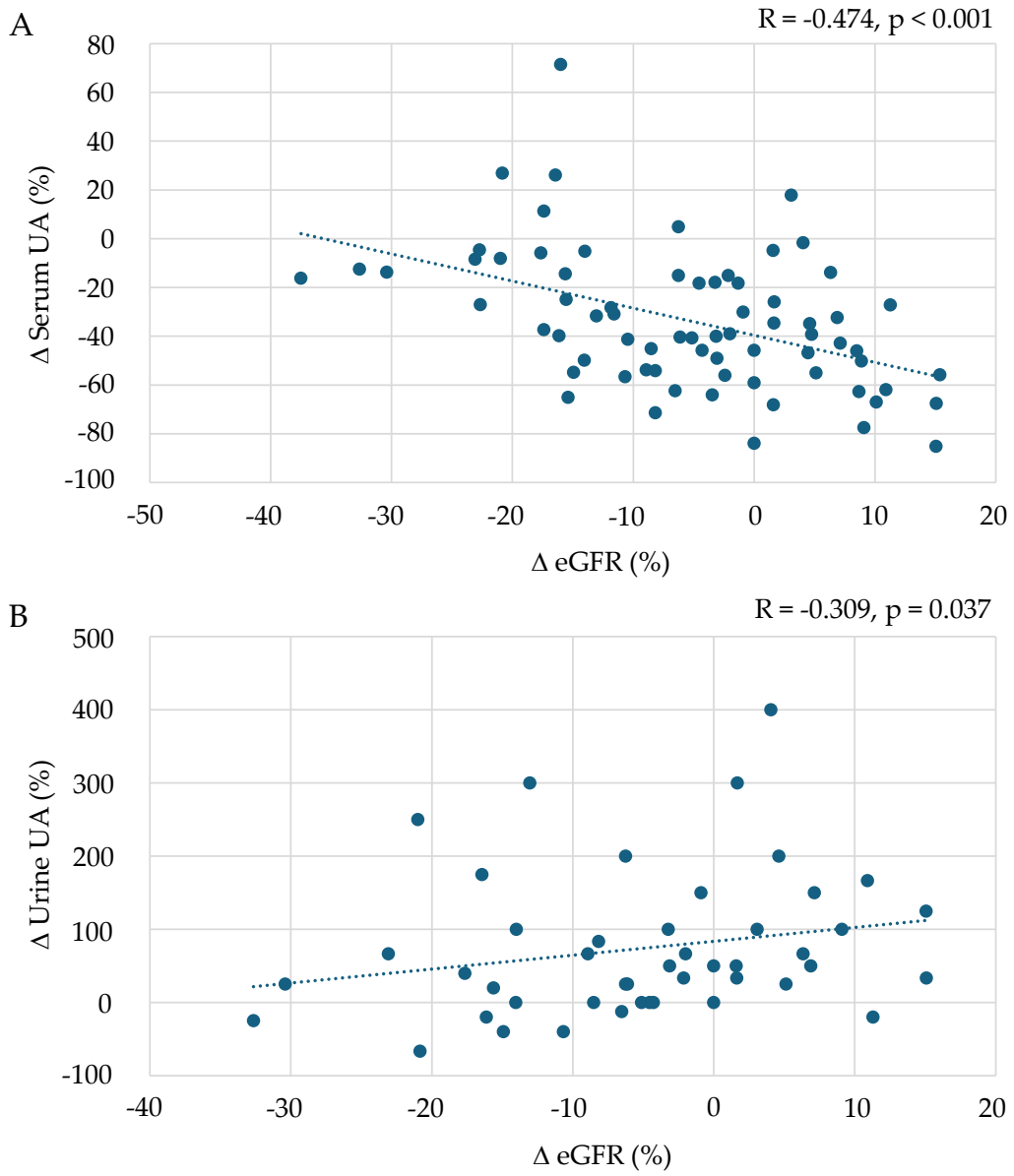

Figure 3. Correlation of % change in eGFR after 24 months from baseline with % changes in serum (A) and urine UA (B) levels after 24 months from baseline.

3.4. The changes in eGFR after the start of dotinurad from baseline

The changes in eGFR after 6, 12, 18, and 24 months from baseline in all patients, patients naïve to UA-lowering drugs, patients who switched from XO inhibitors, and patients who switched from febuxostat were shown in Figure 4. In all patients and patients naïve to UA-lowering drugs, eGFR significantly decreased at 18 and 24 months after the start of dotinurad as compared with baseline. However, such a significant decline in eGFR from baseline was not observed in patients who switched from XO inhibitors, and patients who switched from febuxostat during the observational period. There were no significant differences in eGFR changes among the 4 groups at any observation time.

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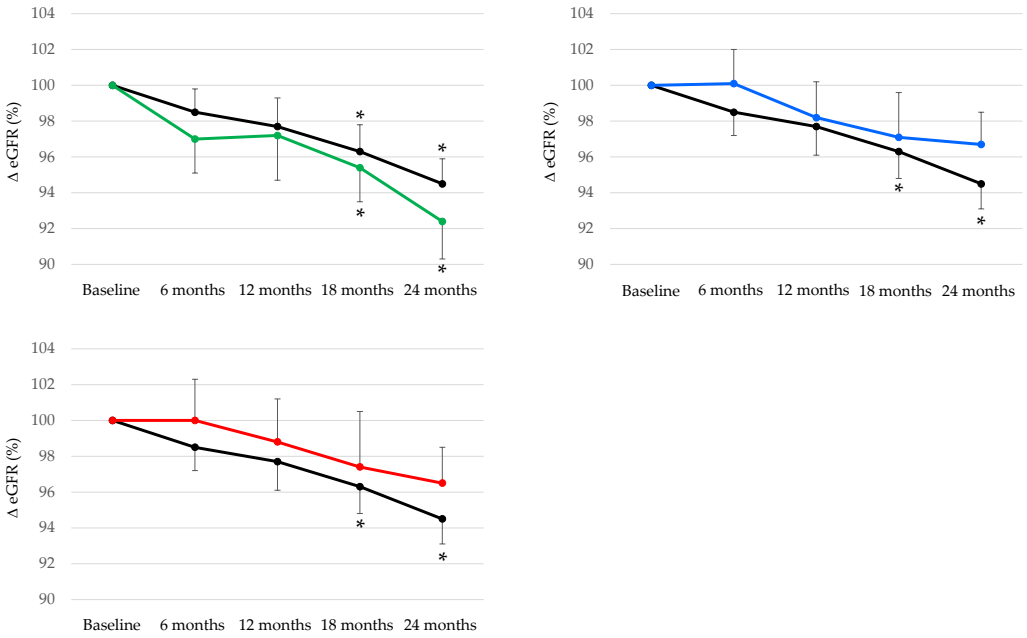

Figure 4. The changes in eGFR after 6, 12, 18, and 24 months from baseline in all patients (black circles and line), patients naïve to UA-lowering drugs (green circles and line), patients who switched from XO inhibitors (blue circles and line), and patients who switched from febuxostat (red circles and line). We set the baseline data of each patient as 100% and evaluated the changes in eGFR as percent changes at each observation period. *$p < 0.05$ vs. baseline. Circles and error bars indicate the mean ± standard error.

4. Discussion

Pharmacologically, dotinurad decreased serum UA levels, by selectively inhibiting URAT1 and decreasing reabsorption of urine UA, which was supported by our result that dotinurad significantly increased urine UA and reduced serum UA during observation time in all patients. Although a significant difference in serum UA was not observed after the switching from XO inhibitors or febuxostat to dotinurad, a significant elevation in urine UA was observed in such patients. This indicates that dotinurad has a UA-lowering effect equivalent to that of XO inhibitors or febuxostat and that dotinurad lowers serum UA through a mechanism different from XO inhibitors.

Dotinurad induced a significant decrease in body weight after 6 and 24 months in all patients, and a significant decrease in body weight was also observed in patients who switched from XO inhibitors. Allopurinol and febuxostat treatment have been reported to induce a significant reduction in body weight, systolic blood pressure, blood glucose, insulin, lipids, and improve renal functions and endothelial function compared to non-treatments in metabolic syndrome model rats [13]. The UA-lowering therapy (febuxostat 20-80 mg/day or benzbromarone 25-50 mg/day) resulted in a decrease in serum UA level accompanied by a decrease in the visceral fat area (VFA) in male gout patients [23]. By multiple regression model, the change in serum UA was identified to be a significant determinant variable of the decrease in VFA (beta, 0.302; $p = 0.001$). URAT1 plays a key role in UA homeostasis in the proximal tubule [24], is also expressed in hepatocytes and adipocytes **[25,26]**, and transports UA into these cells. Elevated intracellular UA levels directly and dose-dependently induce excessive TG accumulation in adipocytes by upregulating the expression of lipogenesis-related proteins and downregulating the expression of lipolysis-related proteins [27]. An in vivo study has shown that benzbromarone, which inhibits URAT1, can reverse this effect by reducing lipogenesis in adipocytes and decreasing TG content [27]. The inhibition of URAT1 by dotinurad may induce a reduction in body weight by inhibiting the entry of UA into adipose tissue. A significant decrease in systolic blood pressure by dotinurad observed in our study may be due to body weight loss or an improvement of endothelial function because URAT1 is also expressed in endothelial cells [28]. High concentration of UA exerts unfavorable effects directly on vascular endothelium via the nuclear

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factor-kappa B (NF-κB) signaling pathway, the process of which requires intracellular uptake of UA by URAT1 [28]. Such an anti-inflammatory effect of dotinurad may also be favorably associated with improving insulin resistance and body weight.

Dotinurad significantly suppressed an increase in body weight and improved insulin resistance in mice fed a high-fat diet (HFD) [29]. The increased uncoupling protein 1 (UCP1) expression and UCP1 activity in brown adipose tissue (BAT) play an important role in the improvement of glucose tolerance and insulin sensitivity [30]. The UCP1 levels in BAT were significantly increased in HFD-fed mice compared to those in normal-fat diet (NFD)-fed mice, and they were further increased by treatment with dotinurad. The uptake of UA can increase oxidative stress in adipocytes, which has recently been recognized as a major cause of insulin resistance [31]. The reactive oxygen species (ROS) levels in BAT were significantly increased in HFD-fed mice, which was significantly reduced by treatment with dotinurad. When cells were exposed to a high concentration of UA, the intracellular UA levels were significantly increased, which was decreased by treatment with dotinurad, indicating that URAT1 actually transports UA into BAT.

Dotinurad significantly improved liver function such as ALT and GGT in all patients, in patients who switched from XO inhibitors and febuxostat. HFD feeding led to the development of macrovesicular steatosis, lobular inflammation, and hepatocellular ballooning, all of which were dramatically attenuated by dotinurad in rats [29]. The chemokine ligand 2 (Ccl2) and tumor necrosis factor α (TNFα) are proinflammatory M1 macrophage markers and key mediators that lead to hepatic lipogenesis and inflammation in HFD-induced obese mice [32,33]. The hepatic expression of Ccl2 and TNFα was increased in HFD-fed mice in comparison with NFD-fed mice, and dotinurad significantly decreased the levels of these markers [29], indicating that the URAT1-selective inhibition significantly improved HFD-induced MASLD by the inhibition of inflammatory genes, which can explain an improvement in liver function observed in our study.

Dotinurad significantly increased serum HDL-C after 6 months in all patients. An improvement in insulin resistance due to reduced body weight may increase HDL-C. Insulin resistance decreases the activity of lipoprotein lipase (LPL), the rate-limiting enzyme of the catabolism of TG-rich lipoproteins such as chylomicron and very-low density-lipoprotein (VLDL) [34]. The formation of HDL is related to the catabolism of TG-rich lipoproteins by LPL [35]. Therefore, reduced LPL activity increases TG-rich lipoproteins, and reduces HDL. Conversely, an increase in LPL activity due to an improvement in insulin resistance reduces TG-rich lipoprotein and increases HDL.

Dotinurad significantly decreased serum non-HDL-C levels at all time points in all patients and patients naïve to UA-lowering drugs. In patients naïve to UA-lowering drugs, a significant decrease in LDL was also obtained at 12, 18, and 24 months after the start of dotinurad. A significant improvement in non-HDL-C was observed after 12 months in patients who switched from febuxostat. Insulin resistance enhances the expression and activity of hormone-sensitive lipase (HSL) in adipose tissue. HSL catalyzes the hydrolysis of TG into fatty acids (FA) [36]. An increased amount of FA enters the liver, leading to the over-production of TG-rich lipoproteins such as VLDL. Insulin resistance increases the expression of sterol regulatory element binding protein 1c (SREBP-1c), which increases FA synthesis [37], and activates SREBP-2, which induces the expression of 3-hydroxy-3-methyl-glutaryl-CoA reductase, the rate-limiting enzyme of cholesterol synthesis [38]. The blocking the influx of UA into the liver by dotinurad improved hepatic inflammation and insulin resistance, which reduced the expression of such lipogenesis-related molecules, resulting in a decrease in VLDL and LDL in our study. FA oxidation primarily occurs in the mitochondria [39], and the entry of FA into mitochondria depends on carnitine palmitoyl-transferase 1 (CPT-1). One of the major regulators of CPT-1 is the peroxisome proliferator-activated receptor (PPAR)α [40–43]. Therefore, activation of PPARα induces the transcription of genes related to FA oxidation [40,44,45]. Insulin resistance is negatively correlated with hepatic PPARα gene expression [45]. Therefore, an improvement in hepatic insulin resistance by dotinurad may increase hepatic FA oxidation, which is also associated with reduced VLDL.

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The definition and staging of CKD are performed by using two components: a decline of eGFR and proteinuria, including microalbuminuria. In the Hisayama Study using a total of 2,059 community-dwelling Japanese subjects aged ≥40 years without CKD were followed for 5 years, CKD was defined as kidney dysfunction (eGFR < 60 ml/min/1.73 m^2) or albuminuria (UACR ≥ 30 mg/g) [46]. Higher serum UA levels were a significant risk factor for the development of both kidney dysfunction and albuminuria in the general Japanese population. In our study, serum UA levels were not correlated with eGFR at baseline and 24 months after the start of dotinurad; however, urine UA levels were significantly and positively correlated with eGFR at 24 months after dotinurad started, suggesting that dotinurad which increases urine UA levels may be beneficially associated with an improvement in eGFR. In the correlation of change in eGFR after 24 months from baseline with change in serum and urine UA levels, change in serum UA was significantly and negatively correlated with change in eGFR, and change in urine UA was significantly and positively correlated with eGFR, indicating that the reduction in serum UA by elevating urinary UA excretion due to dotinurad was associated with an improvement in eGFR. Although a significant decrease in eGFR was observed at some observation times in all patients, a significant reduction in urine albumin was observed after 6 months. Further, although a significant decrease in eGFR was observed at some observation times in patients naïve to UA-lowering drugs, a significant reduction in urine albumin was observed after 6 and 24 months. UA has been demonstrated to have cellular effects inducing oxidative stress, inflammation, and cellular phenotype transition, contributing to glomerulosclerosis and interstitial fibrosis [47]. Therefore, an inhibition of entry of UA to the kidney by dotinurad favorably affected renal function.

A significant decrease in eGFR from baseline was observed in all patients and patients naïve to UA-lowering drugs, whose urine albumin was improved. In patients who switched from XO inhibitors and febuxostat, a significant decline in eGFR was not observed. This indicates that switching from XO inhibitors and febuxostat was beneficial for maintaining eGFR. Renal UA reabsorption is mediated by URAT1 and GLUT9 [48–51]. The ATP-binding cassette transporter G2 (ABCG2) has been identified as a high-capacity UA exporter that mediates renal and intestinal UA excretion [52,53]. ABCG2 is a major transporter of uremic toxins such as indoxyl sulfate (IS) [54]. ABCG2 regulates renal and intestinal excretion of IS and strongly affects CKD survival rates [55]. Serum IS levels increased gradually with decreased renal function [56]. Serum IS concentration is significantly associated with kidney survival because IS induces ROS, resulting in renal injury [57]. Therefore, ABCG2-mediated renal and intestinal excretion of IS is more critical for patients with advanced CKD. Dotinurad, which did not inhibit ABCG2, improved albuminuria. On the other hand, an XO inhibitor, febuxostat, was reported to be a strong ABCG2 inhibitor [58], decreasing renal and intestinal IS excretion, which unfavorably affects renal function. Therefore, switching from febuxostat to dotinurad was beneficial in maintaining eGFR. Dotinurad was reported to significantly improve eGFR in patients with eGFR < 30 [59]. On the other hand, febuxostat reduced eGFR (19.1 mL/min/1.73 m^2 at baseline) by 0.7 mL/min/1.73 m^2 in gout patients with advanced CKD after 4 months [60].

Limitations of the study need to be addressed. This is a cross-sectional study, limiting inferences of causality and its direction. Although we did not change treatments for diabetes, hypertension, and dyslipidemia intentionally during the observation period, we cannot deny the beneficial role of the concomitant assumption of other drugs, including the aspect of synergism and/or the possible interaction between dotinurad and other treatments for metabolic parameters. To elucidate the precise effects of dotinurad on metabolic parameters and renal function, preferentially, RCT, which includes a large number of patients, should be performed in the future.

4. Conclusions

Pharmacologically, dotinurad decreases serum UA levels, by selectively inhibiting URAT1 and decreasing renal reabsorption of UA, which was supported by our result that dotinurad significantly increased urine UA and reduced serum UA. In addition to UA-lowering, dotinurad significantly improved body weight, liver function, and serum lipids, which may be induced by the blocking of

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entry of UA via URAT1 to the liver and adipose tissue. Dotinurad also significantly reduced urine albumin, which may also be induced by inhibition of entry of UA via URAT1 to the kidney. Our study indicates that switching from febuxostat was beneficial for maintaining eGFR. ABCG2 regulates renal and intestinal excretion of IS and strongly affects CKD prognosis. Febuxostat is a strong ABCG2 inhibitor, decreasing renal and intestinal IS excretion, which unfavorably affects renal function. Therefore, the switching from febuxostat to dotinurad, which does not inhibit ABCG2, was beneficial for maintaining eGFR in patients with asymptomatic hyperuricemia.

Author Contributions: H. Y.; Conceptualisation, Supervision, Writing—original draft, review & editing. H. K.; Conceptualisation, Data curation. S. H.; M. H. ; H. A.; Formal analysis, Data curation. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-S-004957-00), and the study was performed in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained by the opt-out approach because this study was a retrospective observational study.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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