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Recent Advances in Hyperuricemia: Effects on Indices of Body and Related Diseases

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Abstract

As a metabolic disease, the epidemiology and clinical research reveal that the incidence of hyperuricemia has been rapidly increasing, which has attracted more attention globally in recent years? In this article, a total of 124 published literatures related to hyperuricemia studies from 1982 to 2020 based on PubMed Database, SinoMed Database, Wanfang Database, Web Of Science Database, CNKI (China National Knowledge Infrastructure) and VIP (China Science and Technology Journal Database) searches are summarized. The purpose of this review is to provide an overview of changes of various indices of the body in hyperuricemia, with an emphasis on diseases associated with hyperuricemia and possible mechanisms, as well as to highlight promising therapy for hyperuricemia. Therefore, people with hyperuricemia should have greater attention to change their diet and lifestyle in an appropriate way, and it's important to provide a general picture for clinical treatment plan and future research directions about hyperuricemia.

Keywords: Hyperuricemia; Indices of the body; Related diseases; Drug therapy

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Introduction

Hyperuricemia (HUA) is a metabolic disorder and it is classically defined as elevated plasma urate levels beyond 420 umol/L in men and 360 umol/L in women [1]. In healthy individuals, about 70% of Uric Acid (UA) is excreted by the kidney and a smaller portion by intestine and bile [2]. Abnormalities in serum uric acid metabolism and its renal under excretion, leading to an excessively increased serum urate concentration, are the major causes of hyperuricemia. Hyperuricemia is modulated by genetic, intrinsic, and environmental factors [3] (Table 1). In recent years, with the rapid economic development and the change of people's living standard, lifestyle factors like an excessive intake of purine abundant foods and alcohol have been strongly associated with the development of hyperuricemia [4,5].

The prevalence of HUA

HUA has emerged as a major public health concern. Epidemiological surveys indicate that the prevalence and incidence of HUA are still increasing globally [6]. For example, the United States National Health and Nutrition Examination Survey showed that a prevalence of HUA of was 20.1% among adults aged 20 and over in America [7]. Another survey in the Chinese population of the southeast coastal region found that the incidence rate of HUA in the physical examination population aged 20 to 50 years was 32.6% (42.5% in men and 22.7% in women) [8]. Yang et al. have reported that the prevalence of HUA was respectively 19.54%, 19.31%, 18.64% and 21.81% from 2015 to 2018 in Lanzhou, China.

Emerging studies found that the prevalence of HUA was certain characteristics and shown in Table 2 [6,9-16]: Younger trend appears: Young people under 30 years old had a higher prevalence of HUA, which could be related to the intake of a large number of sugary drinks and lack of exercise. Gender difference: The HUA prevalence was prominently higher in men than in women. It may be related to a higher clearance of urate in women of fertile age [17] and unhealthy lifestyles in men, such as smoking, drinking and stress. However, in those over 50 years old, the prevalence in females was higher than males, and the difference was statistically significant. The possible reasons may be impaired renal functions and the decreased secretion of estrogen in women after menopause, and some studies showed that estrogen could not only reduce the production of UA, but also directly affect the renal excretion of UA by adjusting the various transporters [9,11,18-21].

Table 1: List of abbreviations.

Abbr	Full name	Abbr	Full name
ALT	Alanine Aminotransferase	IMP	Inosine Monophosphate
AST	Aspartate Aminotransferase	LDL-C	Low Density Lipoprotein Cholesterol
ALP	Alkaline Phosphatase	LDL	Low Density Lipoprotein
ATP	Adenosine Triphosphate	LDLR	LDL Receptor Of Liver Cells
AMP	Adenosine Monophosphate	LPL	Lipoprotein Lipase
AMPK	AMP-Activated Protein Kinase	MCP-1	Monocyte Chemoattractant Protein-1
ABCG2	ATP-Binding Cassette G2	MRP4	Multidrug Resistance Protein 4
AS160	Akt Substrate Of 160 kDa	NFκB	Nuclear Factor-κB
BMI	Body Mass Index	NON-HUA	Non-Hyperuricemia
BP	Blood Pressure	NLRP3	NOD-like Receptor Family Pyrin Domain Containing 3
BUN	Blood Urea Nitrogen	NAFLD	Non-Alcoholic Fatty Liver Disease
CE	Cholesterol Esters	OAT1	Organic Anion Transporter 1
CKD	Chronic Kidney Disease	OAT3	Organic Anion Transporter 3
CVD	Cardiovascular Disease	OAT4	Organic Anion Transporter 4
CM	Chylomicrons	PCSK-9	Proprotein Convertase Subtilisin/Kexin Type-9
CR	Creatinine	PHOSPHO-IRS1	Phospho-Insulin Receptor Substrate-1
DHNB	3,4-Dihydroxy-5-Nitrobenzaldehyde	ROS	Reactive Oxygen Species
DBP	Diastolic Blood Pressure	RAS	Renin-Angiotensin-System
EMT	Epithelial Mesenchymal Transition	SUA	Serum Uric Acid
EPK	Eukaryotic Protein Kinase	SCR	Serum Creatinine
FPG	Fasting Blood Glucose	SBP	Systolic Blood Pressure
FOXO1	Forkhead Box 1	TC	Total Cholesterol
GLU	Blood Glucose	T2DM	Type 2 Diabetes
GFR	Glomerular Filtration Rate	TLR4	Toll-Like Receptor 4
GLUT4	Glucose Transporter Type 4	TLR4	Toll-Like Receptor 4
GLUT9	Glucose Transporter 9	TG	Triglycerides
GGT	Gamma-Glutamyl Transferase	TAC	Tricarboxylic Acid Cycle
HUA	Hyperuricemia	UA	Uric Acid
HBA1c	Glycated Hemoglobin	URAT1	Urate Anion Transporter 1
HDL-C	High Density Lipoprotein Cholesterol	UN	Urea Nitrogen
HDL	High Density Lipoprotein	VLDL	Very Low Density Lipoprotein
HSPG	Heparan Sulfate Proteoglycans	XO	Xanthine Oxidase
HS-CRP	High-Sensitivity CRP	2HPBG	2-Hour Blood Glucose
IR	Insulin Resistance		

The approach for the literature searching

In this article, a total of 124 published literatures related to hyperuricemia studies from 1982 to 2020 were identified through searching PubMed, Web Of Science, SinoMed database, Wanfang database, CNKI (China National Knowledge Infrastructure) and VIP (China Science and Technology Journal Database). The publications are classified and shown in Figure 1. The review focuses on summarizing the changes of various indices of the body in hyperuricemia, diseases associated with hyperuricemia and possible mechanisms. Moreover, current therapies about hyperuricemia will also be discussed. It is useful to obtain valuable and updated information about hyperuricemia for physicians and scientists who work in this field.

The Effects of HUA on Various Indices of the Body

As a metabolic disease, what are the effects of hyperuricemia on various indices of the body? The Body Mass Index (BMI), Blood Pressure (BP), blood lipids, liver function, Blood Glucose (Glu) and renal function will be discussed below, and the relevant literatures reported are summarized in Tables 3-8.

BMI

BMI (kg/m^2) was calculated as body weight divided by body height squared. The relationships between BMI and HUA are summarized in Table 3 [2,3,9,22-35], and the BMI of HUA subjects is significantly higher than those non-Hyperuricemia (non-HUA) group. Zhang et al. [24] carried out a investigated the cross-sectional study among 3,093 participants in Ganzi Tibetan, and found that the

Table 2: The Prevalence of HUA among males and females in different age groups.

Code	Age	Male			Female			Total			P value	References
		N	Cases	Prevalence (%)	N	Cases	Prevalence (%)	N	Cases	Prevalence (%)		
1	18~29	3498	1143	32.68	3865	65	6.86	7363	1408	19.12	P<0.01	[6]
	30~39	6962	2361	33.91	7737	492	6.36	14699	2853	19.41		
	40~49	9428	2698	28.62	7421	469	6.32	16849	3167	18.8		
	50~59	7861	2034	25.87	4056	538	13.26	11917	2572	21.58		
	60~69	2843	544	19.13	1913	322	16.83	4756	866	18.21		
	70~79	1407	320	22.74	1207	316	26.18	2614	636	24.33		
	80~89	624	148	23.72	252	88	34.92	876	236	26.94		
2	18~24	548	116	21.2	684	49	7.2	1232	165	13.4	P<0.01	[9]
	25~34	584	157	26.9	746	35	4.7	1330	192	14.4		
	35~44	756	177	23.4	944	48	5.1	1700	225	13.2		
	45~54	808	178	22	1053	73	6.9	1857	251	13.5		
	55~64	511	70	13.7	753	71	9.4	1264	141	11.2		
	65~74	414	70	16.9	454	77	17	868	147	16.9		
	≥ 75	104	16	15.4	80	20	7.9	8439	36	19.6		
3	<30	20	5	25	16	0	0				P<0.01	[10]
	30~34	748	165	22.06	581	26	4.48					
	35~39	1075	244	22.7	897	32	3.57					
	40~44	905	183	20.22	821	31	3.78					
	45~49	1158	217	18.74	1020	36	3.53					
	50~54	956	156	16.32	816	68	8.33					
	55~59	701	94	13.41	562	65	11.57					
	≥ 60	94	14	14.89	80	11	13.75					
4	≤ 20	56	21	37.5	25	0	0				P<0.01	[11]
	20~30	5175	1119	21.62	3575	142	3.97					
	30~40	10513	2413	22.95	6162	184	2.99					
	40~50	14648	3096	21.14	8182	298	3.64					
	50~60	11636	2052	17.63	7879	644	8.17					
	60~70	4065	579	14.24	3490	424	12.15					
	>70	1688	324	19.19	1502	256	17.04					
5	20~29	679	185	27.25	259	35	13.51	938	220	23.45	P<0.05	[12]
	30~39	631	121	19.18	244	54	22.13	875	175	20		
	40~49	1032	199	19.28	373	56	15.01	1405	255	18.15		
	50~59	896	147	16.41	100	25	25	996	172	17.27		
	≥ 60	178	21	11.8	73	24	32.88	251	45	17.93		
6	<30	462	132	28.6	374	23	6.1	836	155	18.5	P<0.05	[13]
	30~39	647	189	29.2	367	24	6.5	1014	213	21		
	40~49	1149	349	30.4	486	44	9.1	1635	393	24		
	50~59	703	226	31.9	283	36	12.7	992	262	26.4		
	≥ 60	193	37	19.2	108	21	19.4	301	58	19.3		
7	18~24	4499	1514	33.7	6261	531	8.5	10760	2045	19	P<0.01	[14]
	25~34	51137	14859	29.1	52914	2924	5.5	104051	17783	17.1		
	35~44	57110	15400	27	47573	2167	4.6	104683	17567	16.8		
	45~54	49298	11922	24.2	42246	3462	8.2	91544	15384	16.8		
	55~64	27650	5615	20.3	27346	3768	13.8	54996	9383	17.1		
	≥ 65	17187	3605	21	15868	3504	22.1	33055	7109	21.5		

8	16~29	1336	496	37.13	982	99	10.08	2318	595	25.67	P<0.01	[15]
	30~39	1806	687	38.04	1360	18	8.68%	3166	805	25.43		
	40~49	2252	634	28.15	1681	146	8.69	3933	780	19.83		
	50~59	2606	648	24.87	1689	255	15.1	4295	903	21.02		
	60~69	1477	276	18.69	901	184	20.42	2378	460	19.34		
	≥ 70	847	190	22.43	336	92	27.38	1183	282	23.84		
9	18~29	2941	713	24.24	3796	273	7.19	6737	986	1.64	P<0.05	[16]
	30~39	3282	546	16.64	4180	164	3.92	7462	710	9.51		
	40~49	3575	539	15.08	3294	126	3.83	6869	665	9.68		
	50~59	2532	379	14.97	2064	111	5.38	4596	490	10.66		
	60~69	1678	261	15.55	1180	110	9.32	2858	371	12.98		
	70~79	769	113	14.69	582	72	12.37	1351	185	13.69		
	≥ 80	425	66	15.53	374	70	18.72	799	136	17.02		

Table 3: Comparison of BMI characteristics between non-HUA and HUA subjects.

Code	Group	N	Height/cm	Weight/kg	BMI kg/m²	P value	References
1	HUA	24			26.9 ± 4.5	P<0.05	[2]
	Non-HUA	236			24.5 ± 3.8		
2	HUA	1265	163.3 ± 8.5	70.6 ± 12.5	26.4 ± 3.8	P<0.05	[3]
	Non-HUA	10320	160.3 ± 8.1	63.3 ± 10.9	24.6 ± 3.6		
3	HUA	154			24.7 ± 3.5	P<0.05	[9]
	Non-HUA	179			23.4 ± 3.4		
4	HUA	290		75.3 ± 10.6	25.5 ± 3.2	P<0.01	[22]
	Non-HUA	1453		69.4 ± 9.0	23.6 ± 2.7		
5	HUA	294		83 ± 16.1	31.4 ± 5.6	P<0.05	[23]
	Non-HUA	935		78.1 ± 15.6	30.1 ± 5.4		
6	HUA	528	160.85 ± 8.57	69.19 ± 12.76	26.69 ± 4.22	P<0.001	[24]
	Non-HUA	888	159.81 ± 7.82	63.77 ± 11.41	24.95 ± 4.00		
7	HUA	251			29.2 ± 4.5	P<0.05	[25]
	Non-HUA	1727			28.1 ± 4.4		
8	HUA	162		62.9 ± 10.9	26.0 ± 4.1	P<0.05	[26]
	Non-HUA	578		55.9 ± 8.9	23.2 ± 3.3		
9	HUA	114			25.9 ± 6.9	P<0.05	[27]
	Non-HUA	343			21.0 ± 3.0		
10	HUA	339	160.27 ± 8.46	67.56 ± 12.27	26.22 ± 3.93	P<0.05	[28]
	Non-HUA	6127	158.50 ± 7.92	61.59 ± 11.02	24.47 ± 3.75		
11	HUA	708		72.7 ± 0.56	24.6 ± 0.18	P<0.05	[29]
	Non-HUA	16423		62.1 ± 0.07	21.2 ± 0.02		
12	HUA	1130			26.33 ± 3.45	P<0.001	□[30]
	Non-HUA	8090			24.46 ± 3.56		
13	HUA	50			27.09 ± 3.0	P<0.01	[31]
	Non-HUA	50			23.4 ± 3.2		
14	HUA	999	165.5 ± 7.74	71.1 ± 11.1	25.9 ± 3.43	P<0.001	[32]
	Non-HUA	7322	162.2 ± 7.96	63.1 ± 11.5	23.9 ± 5.06		
15	HUA	610			25.59 ± 3.34	P<0.05	[33]
	Non-HUA	3754			24.36 ± 3.42		
16	HUA	108	158.6 ± 8.5	56.3 ± 8.8		P<0.05	[34]
	Non-HUA	201	156.2 ± 10.2	61.9 ± 11.4			
17	HUA	38	169.06 ± 7.83	76.2 ± 16.99		P<0.001	[35]
	Non-HUA	597	163.29 ± 7.79	65.2 ± 10.52			

Table 4: Comparison of BP characteristics between non-HUA and HUA.

Code	Group	N	SBP (mmHg)	DBP (mmHg)	P value	References
1	HUA	1265	146.0 ± 23.5	86.1 ± 12.8	P<0.05	[3]
	Non-HUA	10320	141.3 ± 23.4	81.6 ± 11.5		
2	HUA	290	120.2 ± 14.8	78.5 ± 10.1	P<0.001	[22]
	Non-HUA	1453	115.5 ± 14.2	75.3 ± 9.8		
3	HUA	528	140.06 ± 24.36	86.05 ± 14.51	P<0.001	[24]
	Non-HUA	888	131.86 ± 24.78	79.48 ± 14.84		
4	HUA	339	147.58 ± 24.51	90.91 ± 13.23	P<0.01	[28]
	Non-HUA	6127	142.03 ± 23.06	87.29 ± 11.75		
5	HUA	708	129.8 ± 0.6	75.4 ± 0.4	P<0.05	[29]
	Non-HUA	16423	123.9 ± 0.1	71.4 ± 0.1		
6	HUA	1130	137.00 ± 20.74	82.94 ± 13.13	P<0.001	[30]
	Non-HUA	8090	131.76 ± 21.74	79.03 ± 13.02		
7	HUA	50	125.8 ± 14.4	85.1 ± 11.1	P<0.05	[31]
	Non-HUA	50	114.8 ± 6.5	78.6 ± 5.7		
8	HUA	999	133.9 ± 18.6	80.7 ± 11.7	P<0.01	[32]
	Non-HUA	6422	126.2 ± 19.2	75.9 ± 11.4		
9	HUA	170	144.6 ± 21.4	88.0 ± 11.9	P<0.05	[37]
	Non-HUA	3871	137.5 ± 21.2	83.1 ± 12.1		
10	HUA	4523	131.1 ± 0.25	81.4 ± 0.19	P<0.01	[38]
	Non-HUA	35213	125.1 ± 0.09	77.7 ± 0.07		
11	HUA	7332	130.3 ± 16.4	80.7 ± 10.7	P<0.01	[39]
	Non-HUA	15617	126.5 ± 16.0	77.5 ± 10.2		
12	HUA	375	143 ± 22	81.6 ± 10.8	P<0.05	[40]
	Non-HUA	1246	138 ± 22.6	79 ± 10.6		
13	HUA	24152	129.49 ± 18.22	79.88 ± 12.41	P<0.01	[41]
	Non-HUA	75811	122.20 ± 17.6	74.61 ± 11.67		
14	HUA	358	132.21 ± 17.27	81.57 ± 11.97	P<0.01	[42]
	Non-HUA	1644	126.79 ± 18.21	78.18 ± 11.40		
15	HUA	2867	126 ± 19	77 ± 12	P<0.01	[43]
	Non-HUA	7419	119 ± 18	73 ± 12		
16	HUA	986	124.41 ± 16.56	79.75 ± 10.28	P<0.01	[44]
	Non-HUA	1353	121.19 ± 12.94	78.15 ± 8.88		

risk of developing HUA was 1.116 folds with a 1 kg/m^2 increase in BMI (95% CI: 1.077-1.156) [24]. Kentaro et al. [36] found that there was a still significant correlation between BMI and HUA using a twin study method to exclude the influence of genetic and familial environment factors [36]. Therefore, these studies have suggested that higher BMI levels are related to an increased risk of developing HUA, and people should give more attention to the changes of BMI levels to prevent HUA.

Blood pressure

As shown in Table 4 [3,22,24,28-32,37-44], studies showed that BP level was a significant difference between patients with HUA and healthy people. For example, the Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) of patients with HUA were 1.06 and 1.08 folds compared with non-HUA patients' respectively [24]. Moreover, uric acid level has a stronger association with SBP than DBP. Daniel I. Feig et al. [45] found that SBP and DBP would increase a 14 mmHg and 7 mmHg respectively with each 1 mg/dL (0.5 mg/dL) incremental rise in serum uric acid by investigated 125 children aged 6 to 18 years [45]. Excessive BP can cause the blood vessel wall damage and contribute to hypertension.

Blood lipids

Blood lipids are the general term for neutral fats and lipids in plasma, mainly including Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), and they are essential substances for the basic metabolism of living cells. Related studies between HUA and lipids are summarized in Table 5 [2,9,22,25-27,29-32,36-39,41-43,46-54], and the TC, TG and LDL-C levels are higher in the HUA group than control group, while HDL-C is significantly lower in the patient group. For example, Chu et al. reported that the serum TC and TG increased 2.1 mg/dl and 5.4 mg/dl, respectively, for a 1 mmol/L increase in UA [22]. The experiment conducted by Lanaspa et al. [55] showed that exposed HepG2 cells to an increasing UA concentrations from 4 to 12 mg/dL for 72 h, TG levels were significantly increased

Table 5: Comparison of serum lipid characteristics between non-HUA and HUA subjects.

Code	Group	N	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	P value	References
1	HUA	24	1.84 ± 0.76	4.19 ± 0.88	1.10 ± 0.28		P<0.05	[2]
	Non-HUA	236	1.70 ± 1.04	3.54 ± 1.28	1.22 ± 0.33			
2	HUA	154	1.28 ± 0.77		1.17 ± 0.31		P<0.05	[9]
	Non-HUA	179	1.01 ± 0.56		1.26 ± 0.33			
3	HUA	290	1.40 ± 0.84	5.01 ± 0.89			P<0.001	[22]
	Non-HUA	1453	1.07 ± 0.73	4.70 ± 0.87				
4	HUA	251	2.73 ± 1.55	5.83 ± 1.38		3.51 ± 0.99	P<0.05	[25]
	Non-HUA	1727	2.22 ± 1.37	5.34 ± 1.13		3.27 ± 0.83		
5	HUA	162	1.49 ± 0.75		1.53 ± 0.37		P<0.05	[26]
	Non-HUA	578	1.15 ± 0.60		1.74 ± 0.43			
6	HUA	114		4.87 ± 0.98			P<0.05	[27]
	Non-HUA	343		4.47 ± 0.85				
7	HUA	708		4.69 ± 0.03			P<0.05	[29]
	Non-HUA	16423		4.29 ± 0.01				
8	HUA	1130	2.37 ± 2.39	5.44 ± 1.10		3.43 ± 0.82	P<0.001	[30]
	Non-HUA	8090	1.58 ± 1.26	5.19 ± 1.14		3.25 ± 0.81		
9	HUA	50	2.3 ± 1.2	5.2 ± 0.8	1.1 ± 0.2		P<0.05	[31]
	Non-HUA	50	1.1 ± 0.4	4.7 ± 0.8	1.4 ± 0.3			
10	HUA	999	2.97 ± 2.89	5.14 ± 1.02	1.33 ± 0.32	3.31 ± 0.83	P<0.01	[32]
	Non-HUA	6422	1.78 ± 1.89	4.94 ± 0.97	1.51 ± 0.35	3.15 ± 0.84		
11	HUA	1130	2.37 ± 2.39	5.44 ± 1.10		3.43 ± 0.82	P<0.001	[33]
	Non-HUA	8090	1.58 ± 1.26	5.19 ± 1.14		3.25 ± 0.81		
12	HUA	528	1.76 ± 1.27	5.58 ± 1.19		3.13 ± 0.90	P<0.001	[24]
	Non-HUA	888	1.28 ± 1.01	4.95 ± 1.23		2.71 ± 0.85		
13	HUA	170	3.5 ± 2.8	5.3 ± 1.4	1.2 ± 0.3		P<0.05	[37]
	Non-HUA	3871	1.4 ± 2.8	4.6 ± 1.1	1.3 ± 0.4			
14	HUA	4523	1.86 ± 0.02	5.26 ± 0.01	1.24 ± 0.01	3.06 ± 0.01	P<0.05	[38]
	Non-HUA	35213	1.34 ± 0.01	4.95 ± 0.01	1.33 ± 0.01	2.90 ± 0.01		
15	HUA	7332	2.23 ± 2.29	5.30 ± 0.96			P<0.01	[39]
	Non-HUA	15617	2.2 ± 0.42	5.08 ± 0.87				
16	HUA	24152	2.03 ± 1.69	4.71 ± 0.91	1.13 ± 0.24	2.86 ± 0.77	P<0.01	[41]
	Non-HUA	75811	1.22 ± 1.06	4.47 ± 0.84	1.33 ± 0.30	2.68 ± 0.72		
17	HUA	358	1.82 ± 1.19	5.28 ± 0.92	1.29 ± 0.29	3.07 ± 0.68	P<0.01	[42]
	Non-HUA	1644	1.21 ± 0.84	5.08 ± 0.99	1.46 ± 0.32	2.82 ± 0.71		
18	HUA	2867	2.05 ± 1.39	4.78 ± 0.86	1.16 ± 0.30	3.21 ± 0.81	P<0.01	[43]
	Non-HUA	7419	1.35 ± 0.99	4.54 ± 0.83	1.34 ± 0.34	2.98 ± 0.79		
19	HUA	60	2.16 ± 0.19	5.25 ± 0.59	0.95 ± 0.09	3.31 ± 0.63	P<0.05	[46]
	Non-HUA	60	1.30 ± 0.12	3.64 ± 0.31	1.01 ± 0.06	1.94 ± 0.31		
20	HUA		2.73 ± 2.48	5.50 ± 1.82	1.20 ± 0.67	3.12 ± 1.37	P<0.05	[47]
	Non-HUA		2.23 ± 2.30	5.17 ± 1.35	1.27 ± 0.73	2.99 ± 1.00		
21	HUA	84				2.96 ± 0.88	P<0.05	[48]
	Non-HUA	74				2.58 ± 0.92		
22	HUA	198	2.79 ± 0.81	5.14 ± 0.89			P<0.05	[49]
	Non-HUA	128	0.89 ± 0.36	4.80 ± 0.72				
23	HUA	1328	1.67 ± 1.04		1.26 ± 0.36		P<0.05	[50]
	Non-HUA	3044	1.37 ± 1.00		1.38 ± 0.37			

24	HUA	1157	1.95 ± 1.30	5.36 ± 1.02	1.32 ± 0.29	3.47 ± 0.88	P<0.05	[51]
	Non-HUA	4644	1.49 ± 099	5.24 ± 0.96	1.42 ± 0.30	3.39 ± 0.83		
25	HUA	221	2.583 ± 1.810	5.149 ± 0.971	1.127 ± 0.311	2.302 ± 0.649	P<0.05	[52]
	Non-HUA	1727	1.650 ± 1.466	4.833 ± 0.921	1.135 ± 0.248	2.206 ± 0.617		
26	HUA	46	3.42 ± 0.47	5.41 ± 1.28	0.94 ± 0.12	3.52 ± 0.69	P<0.05	[53]
	Non-HUA	119	1.14 ± 0.28	3.26 ± 1.03	1.68 ± 0.25	2.28 ± 0.46		
27	HUA	200915	1.97 ± 1.73	5.35 ± 1.05	1.24 ± 0.31	3.28 ± 0.80	P<0.05	[54]
	Non-HUA	371259	1.34 ± 1.16	5.07 ± 0.99	1.36 ± 0.34	3.05 ± 0.77		

Table 6: Comparison of liver function characteristics between non-HUA and HUA subjects.

Code	Group	N	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)	P value	References
1	HUA	708	44.2 ± 1.8				P<0.05	[29]
	Non-HUA	16423	20.4 ± 0.2					
2	HUA	1130	28.06 ± 20.61				P<0.001	[30]
	Non-HUA	8090	20.75 ± 15.44					
3	HUA	50	43.8 ± 30.6	27.7 ± 14.8			P<0.01	[31]
	Non-HUA	50	22.6 ± 11.3	20.5 ± 5.9				
4	HUA	24152	31.28 ± 25.5	24.81 ± 13.87	67.86 ± 17.54	44.60 ± 44.91	P<0.01	[41]
	Non-HUA	75811	20.70 ± 20.21	21.01 ± 11.7	63.51 ± 19.35	26.90 ± 30.09		
5	HUA	358	31.56 ± 22.65			40.31 ± 27.82	P<0.01	[42]
	Non-HUA	1644	21.77 ± 15.59			26.20 ± 20.37		
6	HUA	2867	28.46 ± 18.23	21.78 ± 8.58			P<0.05	[43]
	Non-HUA	7419	19.96 ± 13.48	18.91 ± 7.09				
7	HUA	1328	33.2 ± 26.1				P<0.05	[50]
	Non-HUA	3044	30.6 ± 21.1					
8	HUA	40	38.01 ± 28.84	27.04 ± 11.79	67.35 ± 37.11	45.92 ± 29.98	P<0.05	[56]
	Non-HUA	80	26.77 ± 9.82	21.90 ± 10.26	66.81 ± 30.51	30.87 ± 22.89		
9	HUA	483	21.04 ± 13.28	23.21 ± 7.22		30.31 ± 32.89	P<0.05	[57]
	Non-HUA	4825	17.37 ± 8.09	21.63 ± 4.96		19.78 ± 17.13		
10	HUA	40	34.26 ± 26.6	24.90 ± 11.3			P<0.05	[58]
	Non-HUA	20	17.60 ± 13.0	17.70 ± 4.1				

compared with non-exposed cells [55]. These studies indicate that HUA affects the balance of blood lipids and probably leads to hyperlipidemia, obesity, fatty liver and other related diseases for a long time.

Liver function

Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) are mainly distributed in the cytoplasm of hepatocytes, which are used as indicators for evaluating liver damage. Gamma-Glutamyl Transferase (GGT) is a kind of sulfhydryl baseline granulase and can effectively reflect the oxidative stress in patients. The levels of ALT, AST, GGT, ALP are significantly higher in HUA than in non-HUA group in Table 6 [29-31,41-43,50,56-58]. Ogura et al. [29] and Zhao et al. [41] found the ALT and GGT levels of patients with HUA were respectively 2.17 times and 1.66 times higher than those of non-HUA people [29,41]. Chang et al. [59] showed that uric acid levels in serum of patients with HUA were positively correlated with ALT, AST and GGT concentrations [59]. The significantly differences of ALT, AST, ALP, GGT in patients with HUA suggest that the liver cells are damaging and oxidative stress reactions have obviously happened.

Blood glucose

Glu is necessary to cell activities, which must be maintained at a certain level to satisfy the needs of the organs and tissues in body. Glycated Hemoglobin (HbA1c) is an indicator to reflect the average Glu concentrations over 3 months. As show in Table 7 [24,26,30,37-40,54,60-62], a significant difference is observed for Glu, Fasting Blood Glucose (FPG) and HbA1c between non-HUA and HUA subjects. The Glu, FPG and HbA1c levels of patients with HUA were 1.08, 1.24 and 1.69 folds higher than those of healthy people, respectively [37,61]. Moreover, Chen et al. [30] found that UA concentration was positively correlated with FPG, HbA1c by population-based cross-sectional studies [30]. The higher blood glucose and HbA1c concentrations indicate the risk of developing diabetes [63,64].

Renal function

Some indicators are used as evaluating function of kidney, including Serum Creatinine (SCr), Blood Urea Nitrogen (BUN), and Serum Uric Acid (SUA). Compared with the non-HUA group, the indicators in the HUA group are increased significantly, while the Glomerular Filtration Rate (GFR) is obviously lower in Table 8 [3,9,22-25,27,28,31,33,38,40,44,46,47,49,50,58,60,64]. The SUA of

Table 7: Comparison of blood glucose characteristics between non-HUA and HUA subjects.

Code	Group	N	Glu (mmol/L)	FPG (mmol/L)	HbAlc (%)	P value	References
1	HUA	162		5.8 ± 1.42		P<0.05	[26]
	Non-HUA	578		5.46 ± 1.17			
2	HUA	1130		5.73 ± 1.34	5.79 ± 0.94	P<0.001	[30]
	Non-HUA	8090		5.57 ± 1.50	5.68 ± 0.99		
3	HUA	528	5.38 ± 1.49			P<0.001	[24]
	Non-HUA	888	5.18 ± 1.48				
4	HUA	170	5.2 ± 1.4			P<0.05	[37]
	Non-HUA	3871	4.8 ± 1.5				
5	HUA	4523		5.39 ± 0.01		P<0.05	[38]
	Non-HUA	35213		5.20 ± 0.01			
6	HUA	80		6.21 ± 1.16	6.27 ± 1.06	P<0.05	[40]
	Non-HUA	80		5.36 ± 0.82	5.29 ± 1.16		
7	HUA	200915	5.03 ± 1.05			P<0.05	[54]
	Non-HUA	371259	4.98 ± 1.24				
8	HUA	50		5.77 ± 0.97	5.53 ± 0.79	P<0.05	[60]
	Non-HUA	56		5.33 ± 0.53	5.22 ± 0.57		
9	HUA	95		7.89 ± 0.32	7.99 ± 0.47	P<0.05	[61]
	Non-HUA	95		6.36 ± 0.14	4.72 ± 0.24		
10	HUA	30632		5.81 ± 1.11		P<0.05	[62]
	Non-HUA	144063		5.67 ± 1.2			

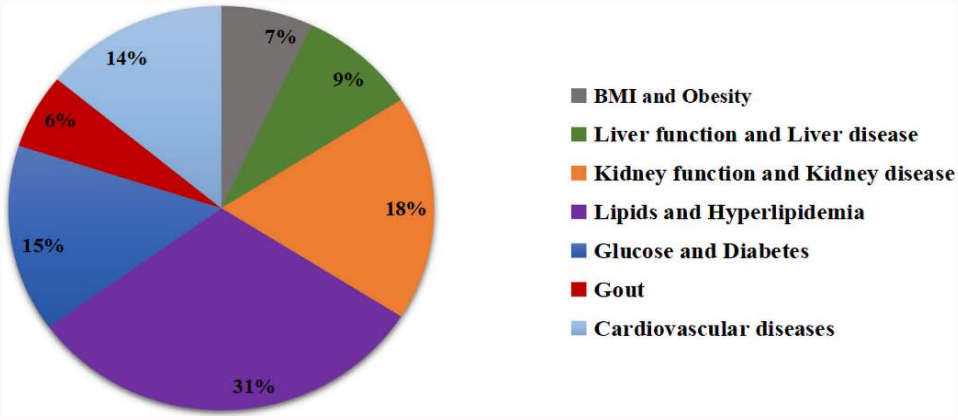

Figure 1: Pie chart of hyperuricemia studies. Based on PubMed Database, SinoMed Database, Wanfang Database, Web of Science Database, CNKI (China National Knowledge Infrastructure) and VIP (China Science and Technology Journal Database) searches performed, we collected a total of 124 articles both in English and in Chinese spanning from 1982 to 2020. After reviewing articles about hyperuricemia, the top three contents are about lipid and hyperlipidemia, kidney function and kidney disease and blood glucose and diabetes, which account for 24%, 14% and 12% respectively.

patients with HUA were 1.82 times higher than those of non-HUA subjects [44]. Wang et al. [44] reported that the GFR of patients with HUA was 0.78 times lower than those of non-HUA people [47]. Zhou et al. [64] also found that the GFR in men and in women decreased respectively by 1.35 and 1.29 times with every increasing 1 mg/dL SUA in the HUA population by a community-based cohort study [64]. Long-term accumulation of SUA because of the decreasing GFR results in kidney damage, leading to various kidney diseases finally.

The Diseases Related to HUA

Substantial studies from laboratory animal research, clinical trials, and epidemiology have strongly indicated that HUA correlates with the development of various diseases, including obesity, cardiovascular disease, hyperlipidemia, non-alcoholic fatty liver, Type 2 Diabetes (T2DM), nephropathy, gout. The contents will be presented and the possible mechanisms will be also discussed below.

Obesity

In recent decades, obesity has attracted more and more attention. BMI over 30 kg/m^2 is defined as obesity according to the WHO standard, while 28 kg/m^2 is used as the cut-off point in Chinese standard [65]. The six-year cross-sectional studies found that overweight (95% CI: 13.0-19.5) and obesity (95% CI: 18.1-25.7) were significantly associated with HUA [40,66]. Another study conducted by Huang et al. [67] also reported that the prevalence of overweight or obesity among HUA patients could reach up to 61.1%.

Table 8: Comparison of renal function characteristics between non-HUA and HUA subjects.

Code	Group	N	BUN (mmol/L)	eGFR (mL/min Per1.73 m^2)	SCr (umol/L)	SUA (umol/l)	P value	References
1	HUA	1265			85.9 ± 44.3	452.1 ± 68.0	P<0.05	[3]
	Non-HUA	10320			70.3 ± 15.4	272.4 ± 63.3		
2	HUA	154			106.08 ± 17.68		P<0.05	[9]
	Non-HUA	179			88.4 ± 17.68			
3	HUA	290				476 ± 47.6	P<0.001	[22]
	Non-HUA	1453				357 ± 71.4		
4	HUA	294				441.0 ± 64.4	P<0.05	[23]
	Non-HUA	935				328.6 ± 85.0		
5	HUA	251			97.24 ± 53.04		P<0.001	[25]
	Non-HUA	1727			79.56 ± 17.68			
6	HUA	114				452.2 ± 77.35	P<0.05	[27]
	Non-HUA	343				279.65 ± 53.55		
7	HUA	339		85.46 ± 18.77	77.67 ± 26.32		P<0.05	[28]
	Non-HUA	6127		93.09 ± 13.73	66.47 ± 17.01			
8	HUA	50			81.2 ± 13.9	470.6 ± 55.0	P<0.01	[31]
	Non-HUA	50			80.6 ± 9.6	325.1 ± 60.6		
9	HUA	610			93.88 ± 35.05	475.80 ± 50.51	P<0.05	[33]
	Non-HUA	3754			70.6 ± 16.34	306.08 ± 59.56		
10	HUA	528			83.68 ± 16.47	462.17 ± 79.88	P<0.001	[24]
	Non-HUA	888			73.43 ± 13.25	308.50 ± 61.28		
11	HUA	4523	5.72 ± 0.02		81.2 ± 0.25		P<0.05	[38]
	Non-HUA	35213	5.31 ± 0.01		74.4 ± 0.08			
12	HUA	375		86.2 ± 13.1	56.5 ± 12.9	300 ± 62	P<0.05	[40]
	Non-HUA	1246		88.4 ± 13	54.4 ± 12.4	262 ± 62		
13	HUA	986	5.63 ± 2.61	87.39 ± 21.45	80.32 ± 45.66	473.02 ± 88.10	P<0.05	[44]
	Non-HUA	1353	5.39 ± 2.48	98.33 ± 32.23	72.98 ± 20.27	259.43 ± 78.46		
14	HUA	60				476 ± 38.66	P<0.005	[46]
	Non-HUA	60				273.7 ± 44.03		
15	HUA			76.8 ± 36.0	108.6 ± 89.4		P<0.05	[47]
	Non-HUA			98.3 ± 36.4	81.1 ± 51.9			
16	HUA	198	5.47 ± 0.83		97.59 ± 10.95	469.87 ± 50.59	P<0.05	[49]
	Non-HUA	128	4.96 ± 0.78		89.68 ± 9.58	279.76 ± 59.84		
17	HUA	1328	6.84 ± 2.42		97.24 ± 44.2		P<0.05	[50]
	Non-HUA	3044	6.19 ± 1.70		88.4 ± 26.52			
18	HUA	40	5.11 ± 1.6	87.87 ± 16.5	90.25 ± 14.6		P<0.05	[58]
	Non-HUA	20	4.18 ± 0.9	103.64 ± 11.3	77.93 ± 10.8			
19	HUA	50				407.88 ± 91.81	P<0.05	[60]
	Non-HUA	56				335.81 ± 80.53		
20	HUA	77	6.8 ± 0.5		94 ± 5	511 ± 54	P<0.05	[64]
	Non-HUA	77	5.4 ± 0.4		72 ± 5	306 ± 86		

It exhibited a gender difference among individuals with HUA that the prevalence of male and female overweight or obesity remained approximately 58.7% and 63.6%, respectively [67]. The elevated SUA level in patients with HUA leads to disorders of lipid metabolism and the adipocytokines changes during fat synthesis, which affects the distribution of adipocyte and makes body shape and weight change, leading to the trend toward obesity.

Cardiovascular disease

Cardiovascular Disease (CVD) is common in modern society. Accumulating evidences obtained from experimental animal studies to clinical trials have demonstrated connections between HUA and CVD. The risk of coronary heart disease in patients with HUA increased 1.28 times compared with non-HUA patients within 10 years (95% CI: 1.09-1.48; P<0.01) [68]. A 1 mg/dl increase in SUA

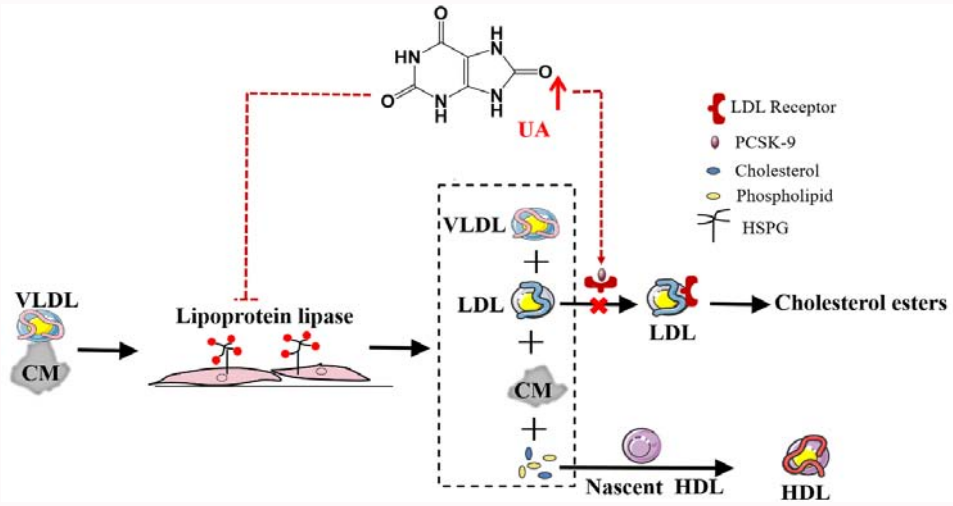

Figure 2: Abnormal blood lipid metabolisms caused by UA. After LPL is combined with Heparan Sulfate Proteoglycans (HSPG) on endothelial cells, it enzymatically hydrolyzes triglycerides in VLDL and CM, and converts them into VLDL, LDL and CM remnants. Elevated UA can inhibit the activity of LPL and increase the level of TG in the blood. UA can also act on LDL receptors to reduce the liver's ability to clear LDL, leading to accumulation of LDL.

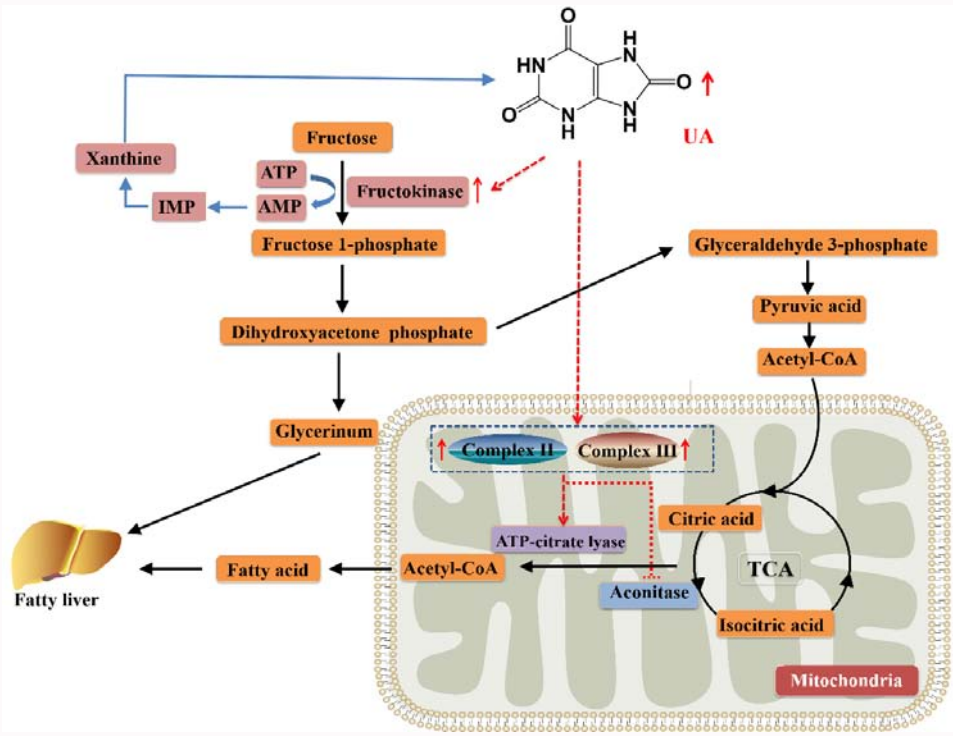

Figure 3: The mechanisms of hyperuricemia leading to non-alcoholic fatty liver. Elevated UA can up-regulate the expression of fructokinase and amplify the lipidation of fructose; Meanwhile, UA can also increase the activity of respiratory chain complexes II and III, leading to mitochondrial oxidative stress and promoting lipid production.

concentration led to a 20% augmented risk of mortality in CVD patients [69]. Another study by Kuwabara et al. [70] evaluated 6887 normotensive Japanese adults (30 to 85 years old) and found that the subjects with HUA (n=783) had a higher cumulative incidence of hypertension over 5 years than those of non-HUA (n=6104; 5.6% *vs.* 2.6%; P<0.001) [70].

At present, it is generally believed that possible mechanisms of HUA causing CVD are as follows: 1) UA could promote the LDL-C oxidation leading to further lipid peroxidation in vessel tissues [71]. Lipid peroxidation was the cause of atherosclerosis [72,73]. 2). For HUA patients, the blood vessel wall and vascular endothelium could be destroyed by deposited uric acid crystals. At the same time, UA could enhance the expressions of platelet growth factors and inhibit the endothelial cell NO synthase, leading to thrombus formation by promoting platelet adhesion and aggregation [74]. 3). UA probably activated the Renin-Angiotensin System (RAS), with influence of sodium steady state and stimulation of vascular smooth muscle cell proliferation, ultimately causing renal vascular disease [75,76]. 4). High UA could promote significantly various inflammatory factors such as Monocyte Chemoattractant Protein-1(MCP-1) and high-sensitivity CRP (hs-CRP) leading to endothelial dysfunction [77].

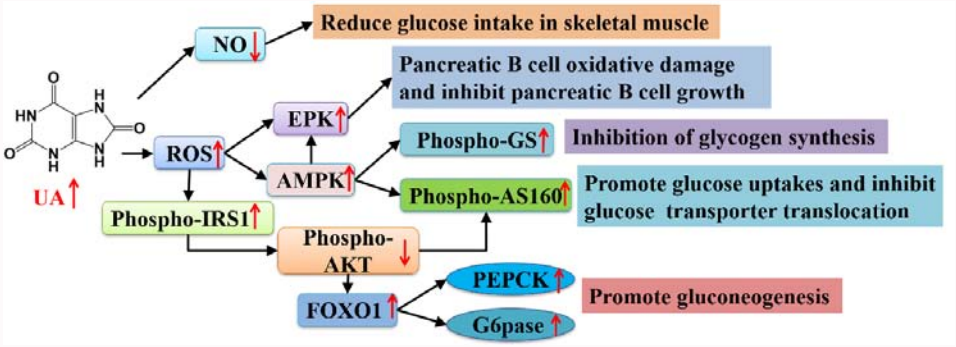

Figure 4: The underlying relationship between HUA and T2DM. Elevated uric acid can activate ROS. ROS can stimulate the EPK and AMPK signaling pathways, leading to oxidative damage of pancreatic B cells and promoting glucose uptake. In addition, ROS can inhibit the phosphorylation of AKT, resulting in gluconeogenesis and the inability of glucose transporter to translocate.

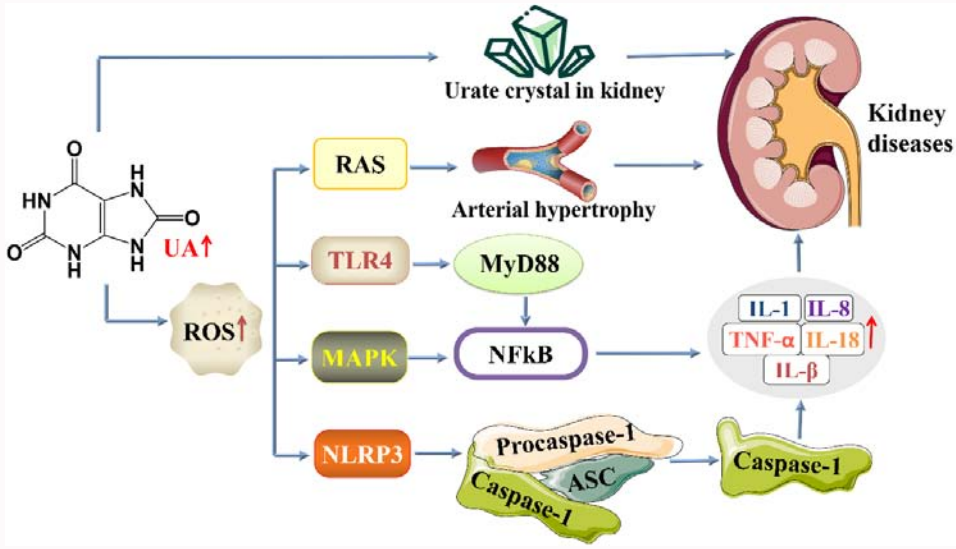

Figure 5: The possible mechanisms of kidney disease caused by HUA. Excess UA forms sodium urate crystals deposited in the kidney leading to nephropathy. On the other hand, elevated UA levels promote the expression of ROS. ROS can further activate RAS, MAPK, Toll-like Receptor 4 (TLR4) and NLRP3 signaling pathways causing arterial thickening and the production of a large number of inflammatory factors.

5). HUA could induce glucose metabolism disorders and further contribute to insulin resistance, which are the risk factors of BP with synergistically promoting the occurrence of hypertension development [78].

Hyperlipidaemia

Numerous studies have shown that HUA is an independent risk predictor for the development of hyperlipidemia. Masanari Kuwabara et al. [79] demonstrated that SUA levels were positively correlated with the cumulative incidence of dyslipidemia in men (R=0.96, P=0.001) and women (R=0.94, P=0.001) over 5 years, and the risk of increased LDL-C was 16% in men and 22% in women for a 1 mg/dL increase in SUA [79]. A longitudinal population-based epidemiological also showed that elevated SUA increased the risks for hypertriglyceridemia and high LDL-C during a 5-year follow-up [80].

Abnormal blood lipid metabolisms caused by HUA are summarized in Figure 2: 1). High levels of SUA can inhibit the activity of Lipoprotein Lipase (LPL). The main function of LPL is the enzymatic hydrolysis of Very Low Density Lipoprotein (VLDL) and Chylomicrons (CM), and the products of enzymatic hydrolysis (phospholipids, cholesterol, etc.) become High Density Lipoprotein (HDL) followed by a series of reactions [81,82]. If LPL activity is inhibited, hypertriglyceridemia would happen with the accumulation of Triglycerides (TG) and the reduction of HDL cholesterol. 2). Elevated SUA can also increase Proprotein Convertase Subtilisin/ Kexin type-9 (PCSK-9) levels, which can degrade Low Density Lipoprotein Receptor (LDLR), and it makes the binding of LDL to LDLR reduced [65,83-86]. At results, blood LDL levels have increased.

Non-alcoholic fatty liver

Evidences emerged from several large epidemiological studies show that HUA is significantly related to Non-Alcoholic Fatty Liver Disease (NAFLD).Yang et al. [87] reported that the independent effect of HUA on NAFLD was stronger in females (RR=2.138, 95% CI: 1.050-4.355) than in males (RR=1.435, 95% CI: 1.021-2.018) by the retrospective cohort study [87]. Another systematic review and meta-analysis studies found increased risk of NAFLD in HUA patients compared with non-HUA people (RR=1.79, 95% CI: 1.55-2.07, P<0.001) [88].

Alternatively, SUA is also an independent risk factor for NAFLD. As shown in Figure 3, the mechanisms of HUA contributing to non-alcoholic fatty liver are discussed: 1). Elevated uric acid can up-

regulate the expression of fructokinase in liver cells, leading to the accumulation of fructose-induced triglycerides [89-91]. On the other hand, the process that fructose is phosphorylated by fructokinase can active the conversion of Adenosine Monophosphate (AMP) deaminase into Inosine Monophosphate (IMP), which leads to producing UA overflowing into the circulation finally [89]. At results, fructokinase and UA form a vicious circle towards fatty liver [92]. 2). High UA can obviously promote the activity of respiratory chain complexes II and III [93], leading to mitochondrial oxidative stress, which can inhibit aconitase in the Tricarboxylic Acid Cycle (TAC) [90]. In addition, UA can activate Adenosine Triphosphate (ATP) citrate lyase leading to lipid regeneration [55].

Type 2 diabetes

Higher levels of SUA have been observed among those with pre-diabetic status or impaired glucose tolerance. A previous meta-analysis of 3305 T2DM cases reported from 11 joint cohort studies (42,834 participants) found that higher SUA level is significantly associated with T2DM development, with 17% increase in T2DM risk for a 1mg/dl increase in SUA [94]. In addition, meta-analysis of prospective cohort studies suggested that the HUA had a significant higher incidence of developing T2DM than those without HUA in youths and elderly people [95].

The underlying relationship between HUA and T2DM is descripted in Figure 4: 1). Increased UA inhibits nitric oxide synthase [96]. The reduction of nitric oxide cuts down the insulin-stimulated glucose intake in skeletal muscles, which leads to insulin resistance [97]. 2). Reactive Oxygen Species (ROS) activated by UA can promote the expression of Eukaryotic Protein Kinase (EPK), causing abnormal glucose metabolism by oxidative damage and growth inhibition of pancreatic B cells [98]. Meanwhile, ROS can also activate AMP-Activated Protein Kinase (AMPK) signaling pathway followed by AMPK phosphorylating AS160 and GS, and glucose uptakes are accelerated and glycogen synthesis is inhibited finally [99]. 3). Activated ROS can stimulate the expression of phospho-Insulin Receptor Substrate-1 (phospho-IRS1) making phospho-AKT inhibited, followed by the activation of Forkhead Box 1 (FOXO1) and phosphorylation of AS160. At results, gluconeogenesis has happened and Glucose Transporter type 4 (GLUT4) protein cannot transport glucose into liver cells, causing glycolysis failed [100,101].

Nephropathy

UA is mainly excreted by kidney. HUA is considered to be a risk factor for kidney disease. Cox regression analysis showed that the hazard ratio of new-onset Chronic Kidney Disease (CKD) in HUA participants was 3.99 (95% CI: 2.59-6.15), indicating a significant correlation between HUA and new-onset CKD [102]. A significant association between UA and renal tubular atrophy and interstitial fibrosis (OR=3.279, 95% CI: 2.037-5.276) was also shown by related histopathological features in renal biopsy [103].

The effects of HUA on kidney function are various. The possible mechanisms of kidney disease caused by HUA are summarized in Figure 5: 1). Sodium urate crystals induced by HUA can be deposited in the kidneys, causing chronic nephropathy and the risk of developing kidney stone [104]. 2). Activated ROS caused by UA can promote RAS to thicken the afferent arteries and interlobular arteries, thereby causing kidney disease. 3). Elevated UA can stimulate ROS to mediate the activation of TLR4-MyD88-NFκB and MAPK-NFκB signaling pathways, and induce production of various inflammatory factors and chemokines such as IL-8, IL-1β, TNF-α in glomerular cells and tubular epithelial cells [105-107]. Long-time high UA levels can cause renal tubular epithelial mesenchymal transition and renal interstitial fibrosis. 4). ROS can also activate NOD-like Receptor Family Pyrin domain containing 3 (NLRP3). NLRP3 can recruit procaspase-1 through the ASC protein and form a complex, which in turn increases the levels of caspase-1leading to inflammatory response [108,109].

Gout

Persistent HUA is an important pathogenesis of gout. Long-term HUA results in the deposition of sodium urate crystals in around joints, especially in the first metatarsophalangeal join. It can stimulate cells to release a variety of inflammatory cytokines and neutrophils. Over time, joints will suffer irreversible damage leading to chronic pain, severe joint deformities and even disability [110]. In a retrospective analysis of a large cohort with an average follow-up time of 7.5 years, the odd ratio of developing gout was respectively 11.2 (CI 3.6-35.2), 107.1 (CI 34.2-334.9) and 624.8 (CI 134.0-2,913.1) in men with mild, moderate and sever HUA [111,112]. It is beneficial to monitor UA levels for the prevention and diagnosis of gout.

Clinical Therapy

Currently, UA-lowing is the main therapy, including the inhibition of UA production and promoting UA excretion. 1). Xanthine Oxidase (XO) has become an effective target for the treatment, and XO inhibitors (allopurinol, hydroxypurinol, febuxostat) can competitively inhibit the activity of XO and reduce the production of UA. However, serious side effects have happened. Efforts are being made to develop new low-toxic or non-toxic XO inhibitors [113]. 3,4-Dihydroxy-5-Nitrobenzaldehyde (DHNB) derived from natural products is a potent inhibitor of XO with low toxicity and good bioactivity [114]. In addition, other new natural products are still studied, such as riparsaponin, genistein (4',5,7-trihydroxyisoflavone), morin, curcumin analogs. 2). The excretion of UA by the kidneys is mainly completed with the assistance of UA transporters, including urate reabsorption transporters and urate excretion transporters [115]. Urate Anion Transporter 1 (URAT1), Organic Anion Transporter 4 (OAT4) and Glucose Transporter 9 (GLUT9) [116] are reabsorption transporters. URAT1 (benzbromarone, probenecid, sulfapyridine, lesinurad), OAT4 (lesinurad) and GLUT9 (robeecid, benzbromarone, losartan) inhibitors have become a research hotspot in recent years [117-121], which can decrease the reabsorption of urate. Organic Anion Transporter 1 (OAT1) and Organic Anion Transporter 3 (OAT3) are urate excretion transporter, and probenecid or lesinurad can prevent uric acid from renal interstitium to renal tubular epithelial cells to reduce serum uric acid by inhibiting OAT1 and OAT3 [122,123]. 3). The use of recombinant uricase is another treatment for reducing UA level by metabolizing UA into allantoin. For example, pegloticase, a mammalian recombinant uricase, has low immunogenicity, greater solubility and can effectively reduce serum UA levels.

Conclusion

HUA is a metabolic disease caused by overproduction or under-excretion of uric acid. It is a major public health issue due to its expanding prevalence, which has attracted more people attention. In this review, the effects of HUA on various indices of the body and related diseases and possible mechanisms. According to the results, HUA is a significant and independent risk factor for the development of various conditions, including obesity, cardiovascular disease, hyperlipidemia, non-alcoholic fatty liver, type 2 diabetes,

nephropathy, gout and many other diseases. HUA people should have greater attention to change their diet and lifestyle in an appropriate way. On the other hand, drug-based treatment is necessary to keep UA concentration below normal level. However, it is worth noting that safety of various hypouricemic agents taken for long-term should be considered. Therefore, it is urgent to develop new drugs with no or much milder adverse effects or new combination therapies at an optimal dose to reduce side-effects and potential drug resistance.

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