Jurnal Sains Kesihatan Malaysia 20 (2) 2022: 149 - 149
DOI : http://dx.doi.org/10.17576/JSKM-2022-2002-14

Kertas Asli/*Original Articles*

Chronic Spontaneous Urticaria in Adult Patients: Evaluating the Effect of Loratadine on Weight and Metabolic Syndrome

(Urtikaria spontan kronik di kalangan pesakit dewasa: penilaian kesan loratadin terhadap berat badan dan sindrom metabolik)

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ABSTRACT

Antihistamine is standard chronic spontaneous urticaria (CSU) therapy. Weight gain is a side effect of concern as prolonged high dose therapy is common. We investigated the effects of 12-weeks loratadine therapy on weight, appetite and parameters of metabolic syndrome (MetS). A cohort study was performed involving CSU patients aged ≥18 years. Patients with diseases or on drugs affecting weight or appetite were excluded. CSU was treated according to standard management. Weight, height, waist circumference (WC), body mass index (BMI) and blood pressure (BP), Urticaria Activity Score 7 (UAS7), Dermatology Life Quality Index (DLQI), hunger and satiety questionnaire, fasting blood sugar (FBS) and fasting lipid profile (FLP) were obtained at baseline, week 6 and week 12. Loratadine cumulative dose were determined. Thirteen (33.33 %) males and 26 (66.67 %) females aged 33.00 (12.00) years participated. Median weight was 62.55 (18.30) kg, BMI 24.60 (6.80) kg/m2, 13(33.33%) patients had normal weight, 12 (30.77%) overweight, 11 (28.21%) obese and 3 (7.69%) underweight. Significant weight gain was observed at week 6, 67.56 ± 16.14 kg vs 68.16 ± 16.95 kg, $p < 0.05$ and 67.56 ± 16.14 kg vs 64.73 ± 14.60 kg, $p = 0.04$ at week 12. Changes in BMI, WC, BP, FBS and FLP were insignificant. Three patients developed MetS. Hunger and satiety scores were unaffected. Loratadine induced weight gain despite no effects on appetite. Weight should be monitored in patients on long term loratadine therapy.

Keywords: Urticaria; loratadine; weight gain; metabolic syndrome; appetite

ABSTRAK

Antihistamin adalah terapi standard penyakit urtikaria spontan kronik (USK). Kesan sampingan kenaikan berat badan perlu perhatian kerana dos tinggi kerap diperlukan. Kami menyiasat kesan rawatan loratadine atas selera makan, berat badan dan parameter sindrom metabolic (MetS) di kalangan pesakit USK. Kajian kohort 12 minggu dijalankan keatas pesakit berusia ≥18 tahun. Pesakit yang mengambil ubat-ubatan atau menghidapi penyakit yang boleh menyebabkan kenaikan berat badan atau selera makan dikecualikan. USK dirawat mengikut standard klinikal. Berat, tinggi, ukurlilit pinggang, index jisim badan and tekanan darah diukur, Skor Aktiviti Urtikaria 7 (UAS7), Indeks Kualiti Hidup Dermatologi (DLQI), soalselidik kelaparan dan kekenyangan, glukosa dan lipid dinilai pada minggu 0, minggu 6 dan minggu 12. Kumulatif dos loratadine dikira. Tiga belas (33.33%) lelaki dan 26 (66.67%) wanita berusia 33 (12.00) tahun menyertai kajian ini. Berat adalah 62.55 (18.30) kg, indeks jisim badan (BMI) 24.60 (6.80) kg/m2, 13 (33.33%) pesakit mempunyai berat normal, 12 (30.77%) berat berlebihan, 11 (28.21%) gemuk dan 3 (7.69%) kekurangan berat. Peningkatan berat badan yang ketara diperhatikan pada minggu ke 6 sebanyak 67.56 ± 16.14 kg vs 68.16 ± 16.95 kg, $p < 0.05$ dan juga pada minggu ke 12 sebanyak 64.16 ± 14.20 kg vs 64.73 ± 14.60 kg, $p = 0.04$. Perubahan BMI, lilitan pinggang, tekanan darah, glukosa dan lipid darah tidak ketara. Tiga pesakit menghidapi MetS. Skor rasa kelaparan dan kekenyangan tidak terjejas. Loratadine menyebabkan kenaikan berat walaupun tiada kesan pada rasa lapar dan kenyang. Berat pesakit yang menggunakan loratadine jangka panjang perlu dipantau.

Kata kunci: urtikaria; loratadine; berat badan; sindrom metabolik; selera makan

INTRODUCTION

Urticaria is defined as development of wheals, angioedema or both. Wheal has three typical features which are itch, swelling surrounded by erythema and a transient nature where each lesion lasts less than 24 hours. Angioedema is characterized by swelling of the deep dermis or mucous membranes with pain or itch that lasts up to 72 hours. Chronic urticaria (CU) is diagnosed when urticaria with or without angioedema is present on most days of the week for longer than six weeks. Spontaneous urticaria has no specific eliciting factors while inducible urticaria can be triggered by environmental stimuli such as heat, cold, pressure, exercise, water, vibration, and sunlight (Zuberbier et al. 2018). CU affects up to 1% of the world population. CSU accounts for 2/3 and the rest are due to chronic inducible urticaria (CIndU) (Balp et al. 2015). Prevalence of CSU is estimated to range from 0.6% to 1.8% (Gaig et al. 2004) (Zazzali et al. 2012) (Lapi et al. 2016) (Seo & Kwon 2019) (Shrestha et al. 2019). Asia has higher point prevalence of CU (1.4%) than Europe (0.5%) and Northern American (0.1%) (Fricke et al. 2020). The Malaysian prevalence of CU or CSU is not available. Urticaria was the fifth most common consulted disease with prevalence of 4.13% in Department of Dermatology, Hospital Kuala Lumpur (Heah Sk et al. 2017). Antihistamine is the first-line treatment of urticaria and angioedema (Chang et al. 2015) (Guillen-Aguinaga et al. 2016). Up to fourfold standard dose of antihistamine is recommended before a second line agent is added (Guillen-Aguinaga et al. 2016).

Histamine is involved in appetite and weight regulation through its effects on the central nervous system and adipose tissue. Histamine in the brain is present within mast cells and as neurotransmitters. Intra-ventricular administration of H1 receptor antagonist has been shown to cause increased food intake in mice (Mercer et al. 1994). Meanwhile, inhibition of H1 receptor downregulates leptin, a hormone produced by adipocytes that facilitates histamine release from the hypothalamus to reduce food intake and increase energy expenditure (Jørgensen et al. 2007) (Miller 2019). Histamine also plays a role in fat metabolism by promoting lipolysis through central stimulation of the sympathetic nervous system (Jørgensen et al. 2007) (Miller 2019). Prolonged use of antihistamine has the potential to disrupt this appetite and weight regulatory mechanisms. Higher weight, BMI and WC among antihistamine users was reported by the National Health and Nutrition Examination Survey (NHANES) (Ratliff et al. 2010). However, there were no data on the indications for treatment and duration of antihistamine use in this survey.

CSU patients are on high doses of anti-histamine for a prolonged duration up to years. There is very limited data on the effect of anti-histamine on appetite, weight gain and the MetS. Knowledge on these aspects will help in better long-term management of CSU patients.

Our study primary objective was to determine the effect of 12-week loratadine treatment on body weight, blood glucose, serum lipids, MetS and appetite in patients with CSU. Secondary objective was to determine the association between cumulative dose of loratadine with appetite and weight gain.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT SELECTION

We performed a 12 weeks prospective cohort study from January - July 2021 at dermatology clinics of two tertiary hospitals. Patients were recruited by convenience sampling method based on availability and willingness of patients to participate. Sample size was calculated by using Select statistical services sample size calculator.[R] The expected odds ratio for overweight and obesity was derived from Ratliff et all (Ratliff et al. 2010) and the expected prevalence of the outcome in absence group is derived from National Health and Morbidity Survey 2019 which states that 50.1% of Malaysians are overweight and obese (Institute for Public Health 2020). Total sample size taking into account 20% drop out rate is 101 subjects. Inclusion criteria was patients with CSU aged ≥ 18 years. Patients were excluded if they have taken daily antihistamine for ≥ 4 weeks, on drugs known to affect weight or appetite, on traditional treatments or supplements with unknown ingredients, has poorly controlled comorbidities that may affect weight or appetite such as diabetes mellitus, hypo- or hyperthyroidism and malignancy, eating disorders, patients with intention to lose or gain weight, pregnancy, lactation, and those unable to read and understand Malay or English. Patients were withdrawn from the study if medications known to affect appetite or weight were commenced, required systemic steroid or second line CSU therapy.

STUDY METHODOLOGY

Patients were advised at baseline not to start on a new diet or exercise regime throughout the study duration, this advice was repeated at each subsequent visit. They were asked regarding any change in dietary habit, daily activities and enrolment in weight gain or reduction programme at each visit. CSU was managed according to standard clinical management with loratadine as the antihistamine of choice due to its availability. Loratadine is typically started with 10mg to 20mg daily, if urticaria still uncontrolled the dose

is increased to 30mg or a maximum of 40mg daily (Zuberbier et al. 2018). Demographics and clinical characteristics were obtained by face-to-face interview and medical records. Anthropometric measurements including weight, height, WC, BMI, and BP were obtained. UAS7 (Hawro et al. 2018) and DLQI (Finlay & Khan 1994) (Basra et al. 2008) (Hongbo et al. 2005) were used to assess urticaria severity. UAS7 is a validated urticaria severity assessment tool that evaluates itch and number of lesions. Patients score their itch severity and count number of lesions daily for 7 days. The DLQI is a simple self-administered validated questionnaire designed to measure health-related quality of life of patients suffering from skin diseases. DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their quality of life over the last week. A bilingual hunger and satiety questionnaire consisting of 41 questions related to 5 factors: mental hunger, physical hunger, mental fullness, physical fullness and food liking to evaluate changes in appetite was used in this study (Karalus 2011). The English version of the questionnaire was validated (Karalus 2011), forward and backward translation with preliminary pilot testing were performed for the Malay version (Chan & Safii 2018). Anthropometric measurements, UAS7, DLQI and hunger and satiety questionnaire were evaluated at each visit: week 0, week 6 and week 12. Cumulative loratadine dose were determined at week 6 and week 12. FBS, FLP, were performed at week 0. Two patients were indicated for additional TSH and autoimmune screening test. FLP consist of total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglyceride (TG). FBS and FLP were repeated at week 6 for patients were unable to complete the study up to week 12, otherwise the tests were performed at week 12. MetS diagnosis was based on Joint Interim Statement (JIS) (K.G.M.M. Alberti et al. 2009) (Ramli et al. 2013). Diagnostic criteria include: WC ≥ 90cm (for males), WC ≥ 80cm (for females), systolic blood pressure (SBP) ≥ 130 and/or diastolic blood pressure (DBP) ≥ 85mmHg or on treatment for hypertension, TG ≥ 1.7 mmol/L or on treatment for TG, reduced HDL < 1mmol/L (for males) and < 1.3mmol/L (for females) or on treatment for HDL, FBS ≥ 5.6mmol/L or on treatment for elevated glucose. Patient who fulfilled 3 or more criteria was diagnosed with MetS.

STATISTICAL ANALYSIS

Data was tabulated and analysed using IBM® Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. Descriptive data were presented as number and percentages for categorical variables. Mean with standard deviation (SD) was used for normal distributed continuous data. Median with Interquartile range (IQR) was used for skewed continuous data. Paired t, One Way ANOVA, Wilcoxon Signed Ranks and Kruskal Wallis test were used to analyse numerical data where applicable. While, McNecar test was used to analyse categorical data. A p-value of <0.05 was consider as statistically significant.

ETHICAL CONSIDERATIONS

Ethical approvals were obtained from the Research Ethics Committee, National University of Malaysia (FF-2020-797) and Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-20-2744-57481). Informed consent was obtained from all study participants.

RESULTS

DEMOGRAPHIC, CLINICAL AND ANTHROPOMETRIC CHARACTERISTICS

A total of 39 patients with CSU consisting of 13 (33.33 %) males and 26 (66.67 %) females were enrolled in this study. At week 6, seven patients were withdrawn from the study; 1 received systemic steroids, 1 became pregnant, 1 was diagnosed with hyperthyroidism, 3 were unable to comply with study visit due to COVID-19 movement control order and 1 patient withdrew her consent. At week 12, twelve more patients were excluded, 1 patient embarked on a weight reduction programme and 11 patients were unable to comply with study visits due to COVID-19 movement control order. Thirty-two patients completed the study up to week 6, 20 patients were followed up until week 12. Results of week 0 and 6 were for on N=32, while N=20 for results of week 12.

The study population was predominantly females with female to male ratio of 2: 1. Almost two third of the patients were Malay (61.54 %), one quarter were Chinese (28.20 %), the rest were Indian (10.26 %). Median age was 33 (12.00) and median age of CSU onset was 31 (15.00) years. Time to CSU diagnosis was 5 (22.00) months. Eleven patients had atopic diseases, half of them (6) had 2 concomitant atopic diseases. The most common atopy was bronchial asthma 9 (23.08 %), followed by allergic rhinitis 5 (12.82 %), atopic eczema 2 (5.13 %) and allergic conjunctivitis 1 (2.56 %). Thirteen patients had family history of atopic disease, bronchial asthma was most common 11 (28.21 %), followed by equal number of

allergic rhinitis, atopic eczema 3 (7.69 %) and allergic conjunctivitis 1 (2.56 %). Only 5 (12.8%) patients have family history of chronic urticaria.

Median weight was 62.55 (18.30) kg while BMI was 24.60 (6.80) kg/m^2. Thirteen patients (33.33%) were of normal weight, 12 (30.77%) overweight, 11 (28.21%) obese and 3 (7.69%) underweight. Mean WC was 88.82 ± 12.49 cm for males and 84.47 ± 16.25 cm for females. There were 5 (38.47 %) male and 15 female (57.69 %) patients with central obesity. Mean SBP was 122.95 ± 14.37 mmHg and mean DBP was 80.23 ± 10.30 mmHg. Median FBS was 5.22 (0.70) mmol/L, TG 1.00 (0.70) mmol/L and HDL 1.55 ± 0.59 mmol/L. Seven (17.94%) patients had MetS. Demographic, clinical and anthropometric characteristics of the study population are summarized in Table 1.

EFFECT OF LORATADINE ON WEIGHT, BLOOD GLUCOSE, SERUM LIPIDS AND METS.

Significant weight gain was observed at week 6 and week 12. Baseline weight was 67.56 ± 16.14 kg, at week 6 weight increased to 68.16 ± 16.95 kg with $p<0.05$. Weight at week 12 was 64.73 ± 14.60 kg with $p=0.04$ compared to baseline. Greater weight gain was observed from week 0 to week 6 compared to from week 6 to week 12. Increments in BMI, WC, SBP, DBP, FBS, TG and HDL after 6 and 12 weeks of loratadine treatment were not significant. These findings are summarized in Table 2. The number of patients that fulfilled diagnostic criteria for MetS remained unchanged at week 6. A total of 3 patients developed MetS at week 12, however this finding was not significant with $p= 0.25$. The pre-existing 3 MetS patients remained MetS.

Table 1 Demographic, clinical and anthropometric characteristics

Characteristics	N=39 n (%) or median (IQR) or mean ± SD
Age, in years	33.00 (12.00)
Gender, n (%)	
Male	13 (33.33)
Female	26 (66.67)
Ethnicity, n (%)	
Malay	24 (61.54)
Chinese	11 (28.20)
Indian	4 (10.26)
Duration of urticaria, in months	8.00 (20.00)
Time to diagnosis, in months	5.00 (22.00)
Age of urticaria onset, in years	31.00 (15.00)
Age of diagnosis, in years	32.00 (15.00)
Personal history of atopy, n (%)	
Allergic rhinitis	5 (12.82)
Allergic conjunctivitis	1 (2.56)
Atopic eczema	2 (5.13)
Bronchial asthma	9 (23.08)
Family history of atopy, n (%)	
Allergic rhinitis	3 (7.69)
Allergic conjunctivitis	1(2.56)
Atopic eczema	3 (7.69)
Bronchial asthma	11 (28.21)
Family history of Urticaria, n (%)	5 (12.82)
Height, in cm	161.51 ± 7.25
Weight, in kg	62.55 (18.3)
BMI, kg/m2	24.60 (6.80)
BMI categories, n (%)	
Underweight (<18.5) (n)	3 (7.69)
Normal (18.5-22.9) (n)	13 (33.33)

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Overweight (23.0-27.5) (n)	12 (30.77)
Obese (>27.5) (n)	11 (28.21)
Waist circumference (WC), in cm (total)	85.92 ± 15.08
WC, Male	88.82 ± 12.49
WC, Female	84.47 ± 16.25
Systolic blood pressure (SBP), in mmHg	122.95 ± 14.37
Diastolic blood pressure (DBP), in mmHg	80.23 ± 10.30
Fasting blood sugar (FBS), in mmol/L	5.22 (0.70)
Fasting Triglyceride, in mmol/L	1.00 (0.70)
Fasting HDL-C, in mmol/L	1.55 ± 0.59
Presence of metabolic syndrome, n (%)	7 (17.90)

Table 2: Effect of loratadine treatment on weight, blood glucose and serum lipids in patients with chronic urticaria.

	Week 0 vs Week 6 (N=32) Mean ± SD or Median (IQR)			Week 0 vs Week 12 (N=20) Mean ± SD or Median (IQR)			Week 6 vs Week 12 (N=20) Mean ± SD or Median (IQR)		
Parameter	Week 0	Week 6	*P* value [e]	Week 0	Week 12	*P* value [e]	Week 6	Week 6	*P* value [e]
Weight, kg	67.56 ±16.14	68.16 ±16.95	<0.05	64.16 ±14.20	64.73 ±14.60	0.04	64.59 ±14.62	64.73 ±14.60	0.67
Body mass index, (kg/m^2)	25.71 ±6.04	25.9 ±6.30	0.08	24.59 ±5.24	24.77 ±5.38	0.15	24.72 ±5.28	24.77 ±5.38	0.70
Waist circumference, cm	86.88 ±15.19	87.52 ±16.05	0.08	84.25 ±13.73	84.56 ±14.09	0.42	84.67 ±14.12	84.56 ±14.09	0.80
Systolic blood pressure, mmHg	121.5 ±13.71	121.8 ±14.52	0.87	119. ±15.19	121.3 ±14.16	0.44	118.6 ±14.96	121.3 ±14.16	0.19
Diastolic blood pressure, mmHg	80.38 ±10.55	81.00 ±10.38	0.69	79.00 ±10.88	78.85 ±13.00	0.95	77.85 ±0.82	78.85 ±13.00	0.63
Fasting blood sugar, mmol/L	5.60 (1.40)	4.97 (1.60)	0.48[a,f]	5.06 (0.6)	5.0 (0.9)	0.58[b,f]	-	-	n/a
Triglyceride, mmol/L	1.11 ±0.39	1.10 ±0.38	0.90[a]	1.19 ±0.53	1.19 ±0.44	0.98[c]	-	-	n/a
HDL-C, mmol/L	1.47 ±0.26	1.43 ±0.43	0.66[a]	1.46 ±0.34	1.40 ±0.31	0.37[d]	-	-	n/a

[a] Comparison among 9 patients [b] Comparison among 20 patients [c] Comparison among 19 patients. [d] Comparison among 18 patients [e] Paired t test [f] Wilcoxon Signed Rank test

Table 3 Effect of loratadine treatment on hunger and satiety scores

Hunger and satiety scores Mean ± SD										
Week 0 vs Week 6 N=31				Week 0 vs Week 12 N=19				Week 6 vs Week 12 N=19			
Week 0	Week 6	Mean difference	*p* value [a]	Week 0	Week 12	Mean difference	*p* value [a]	Week 6	Week 12	Mean difference	*p* value [a]
Mental hunger											
109.0 ±32.22	111.6 ±28.33	2.65	0.30	107.5 ±35.49	109.1 ±31.14	1.53	0.73	110.4 ±29.45	109.1 ±31.14	-1.31	0.56

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Physical hunger											
32.45 ±11.42	33.16 ±10.32	0.71	0.65	33.32 ±13.09	31.47 ±11.57	-1.85	0.38	32.47 ±10.98	31.47 ±11.57	-1.00	0.46
Total Hunger											
141.4 ±42.30	144.8 ±36.88	3.36	0.38	140.8 ±47.22	140.5 ±41.40	-0.31	0.96	142.8 ±39.25	140.5 ±41.40	-2.31	0.50
Mental fullness											
23.39 ±11.28	23.87 ±11.11	0.48	0.68	23.26 ±11.30	23.68 ±10.37	0.42	0.85	23.68 ±10.54	23.68 ±10.37	0.00	1.00
Physical fullness											
5.26 ±6.06	6.52 ±7.25	1.26	0.03	5.37 ±6.42	6.00 ±7.73	0.63	0.43	7.00 ±7.64	6.00 ±7.73	-1.00	0.15
Total Fullness											
28.65 ±15.00	30.39 ±16.04	1.74	0.23	28.63 ±16.09	29.68 ±16.89	1.05	0.69	30.68 ±16.45	29.68 ±16.89	-1.00	0.50

[a] Paired t test

Table 4 Relationship between cumulative dose of loratadine with weight and weight gained

Duration of therapy	Weight (kg) Mean ± SD			*p* value [a]
	Low dose ≤840mg (10mg/day)	Moderate dose 850-1680mg (20mg/day)	High dose 1690-3360mg (30-40mg/day)	
Week 6	73.40 ± 20.16	63.45 ± 12.69	70.79 ± 16.18	0.33
Week 12	67.85 ± 17.62	59.83 ± 10.65	68.13 ± 16.62	0.50
	Weight gained (kg)			
	Low dose ≤840mg (10mg/day)	Moderate dose 850-1680mg (20mg/day)	High dose 1690-3360mg (30-40mg/day)	
Week 6	0.38 ± 2.18	0.72 ± 1.44	0.69 ± 1.33	0.88
Week 12	0.26 ± 1.16	0.51 ± 1.06	0.95 ± 1.24	0.58

Table 5 Relationship between cumulative dose of loratadine with hunger and satiety scores

Hunger and satiety parameters	Hunger and satiety score Mean ± SD			*p* value [a]
	Low dose ≤840mg (10mg/day)	Moderate dose 850-1680mg (20mg/day)	High dose 1690-3360mg (30-40mg/day)	
Mental Hunger				
*W*6	112.10 ± 31.98	110.79 ± 15.42	112.71 ± 16.73	0.99
*W*12	109.50 ± 26.89	115.86 ± 17.71	100.83 ± 47.39	0.71
Physical Hunger				
*W*6	34.80 ± 9.92	33.00 ± 7.48	31.14 ± 15.95	0.78
*W*12	34.00 ± 9.14	31.86 ± 6.28	28.50 ± 18.23	0.73
Mental Fullness				
*W*6	24.20 ± 9.01	24.07 ± 12.68	22.71 ± 12.05	0.95
*W*12	26.50 ± 9.52	22.14 ± 8.09	22.67 ± 14.28	0.74
Physical Fullness				
*W*6	3.00 (10) [b]	1.50 (14) [b]	6.00 (15) [b]	0.65[c]
*W*12	5.00 (9) [b]	0.00 (10) [b]	5.00 (16) [b]	0.39[c]
Food liking				
*W*6	21.20 ± 8.03	18.86 ± 5.43	19.14 ± 9.01	0.74
*W*12	19.33 ± 7.31	18.86 ± 4.45	16.00 ± 9.06	0.68

EFFECT OF LORATADINE ON HUNGER AND SATIETY

Table 3 showed the effect of loratadine on hunger and satiety scores in the domains of mental and physical hunger, and mental and physical fullness. There were no significant changes in all domains at week 6 and week 12 except for increased in physical fullness between week 0 and week 6.

RELATIONSHIP BETWEEN LORATADINE CUMULATIVE DOSE WITH HUNGER, SATIETY AND WEIGHT.

Weight gain was not significantly associated with cumulative loratadine dose. There was no significant association between loratadine dose with hunger and satiety scores. Patients on moderate and high dose loratadine experienced neither increment of mental hunger and physical hunger nor decrement of mental fullness and physical fullness significantly at week 6 and week 12. Weight gain was not associated with appetite. These results are shown in Table 4 and 5.

EFFICACY OF LORATADINE FOR CSU AND SIDE EFFECTS.

Loratadine significantly reduced UAS7 from week 0 to week 6, $p<0.01$, and week 0 to week 12 $p<0.01$. DLQI significantly improved from week 0 to week 6 $p<0.01$, and week 0 to week 12 $p<0.01$. All categories of DLQI were markedly improved from very much or a lot affected into little or not at all. These improvements are plotted in Figure 1. There was significant correlation between UAS7 and total DLQI score at week 0, week 6 and week 12 with $p<0.01$. The correlation was of moderate and direct relationship with r=0.731, r=0.717 and r=0.794 at week 0, 6 and 12, respectively.

A total of 5 patients encountered side effects of treatment. Three (9.4%) complained of somnolence, and 3 (9.4%) had dry mucosae. One (3.1%) patient had both somnolence and mucosal dryness. None experienced urinary retention. Somnolence did not seem to be dose related, the cumulative loratadine dose in the 3 patients were 790mg, 810mg and 3300mg. Similarly, mucosa dryness occurred in patients with varying loratadine cumulative dose, 840mg, 2800mg and 3300mg. Side effects were mild and did not require any change in treatment.

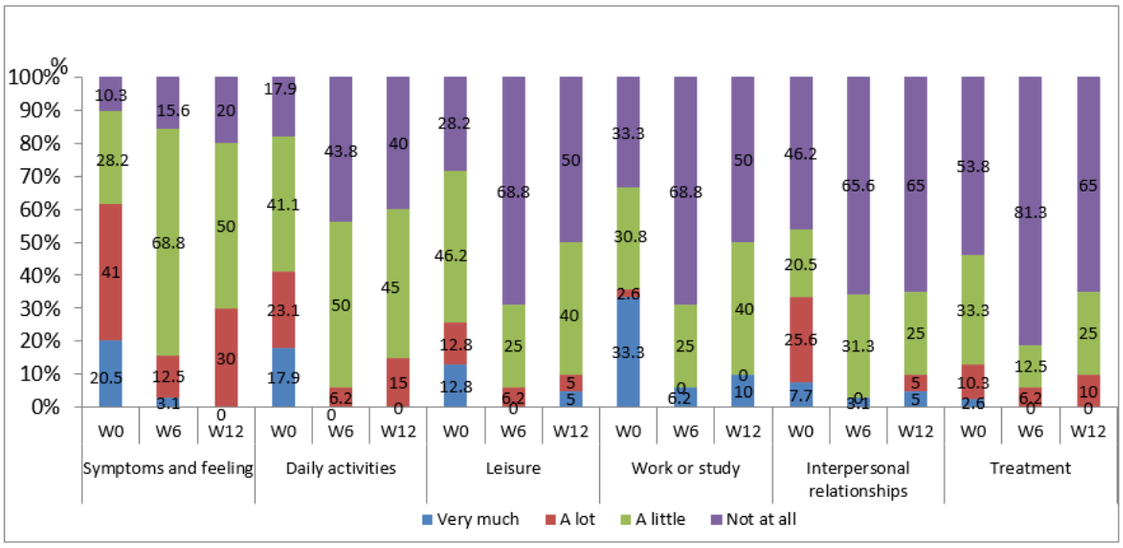

Figure 1 Comparison DLQI category in CSU patient at week 0, week 6 and week 12 loratadine treatment.

DISCUSSION

OVERWEIGHT, OBESITY AND CSU

Obesity is associated with multiple comorbidities and physical as well as psychological health complications. The Malaysian National Health and Morbidity Survey in 2019 estimated that 50.1% of Malaysians were overweight and obese (Institute for Public Health 2020). There was a predominance of middle aged (55-59 years) overweight and obese females (Institute for Public Health 2020).The prevalence of overweight and obese in our study cohort was similar, although there were more females and the patients were younger.

Obesity is increasingly recognized as an association and risk factor for CSU (Lapi et al. 2016) (Institute for Public Health 2020) (Choudhary & Shrestha 2020) (Kim

et al. 2019) (Zbiciak-Nylec et al. 2018). Up to 69% of CSU patients were reported to be obese and overweight (Choudhary & Shrestha 2020). An analysis of the Korean National Health Insurance Service (NHIS) database 2002-2015 found hazard ratios for CSU HR 1.05 (95%CI,1.03-1.07) in overweight and HR 1.06 (95%CI,1.04-1.09) in obese patients while the incidence rates were 2.41 and 2.48 respectively (Kim et al. 2019). The Italian Health Search IMS Health Longitudinal Patient Database reported HR 1.4 (95% CI, 117-167) for CSU in obese patients (Lapi et al. 2016). These population database analyses established the association between obesity with CSU.

THE EFFECT OF ANTIHISTAMINE ON WEIGHT

The NHANES reported higher weight in antihistamine users compared to age and gender matched controls (Ratliff et al. 2010). Increment in BMI percentile per year and BMI z-score among paediatric antihistamine users has also been reported (Saad et al. 2020). Weight gain was observed in patients with seasonal allergic rhinitis treated with loratadine (Chervinsky et al. 1994). We demonstrated significant weight gain with loratadine therapy. Greater weight gain was observed from initiation of therapy till week 6 and continued to increase at a lower rate till week 12. These findings suggest antihistamines may cause weight gain. However, a previous study showed no weight gain with second generation antihistamines loratadine and clemastine in patients with hay fever (Irander et al. 1990). Loratadine dose does not seem to have an impact on weight gain as demonstrated by our results. Antihistamine dosage is important in CSU as patients may receive up to fourfold standard dose as part of CSU management. The effect of antihistamine dose on weight and parameters of the MetS has not been previously reported to the best of our knowledge.

THE EFFECT OF ANTIHISTAMINE ON APPETITE AND METS

We investigated the influence of loratadine on appetite to further clarify its effect on weight gain. There was no change in appetite despite weight gain, as mental and physical hunger scores were not significantly raised, and mental fullness not significantly reduced. Loratadine has a high affinity for peripheral H1-receptors with no blood-brain barrier permeability (Welch et al. 2002). Loratadine most likely affects weight through its action on peripheral rather than central regulatory mechanisms of weight and appetite control, thus its lack of effect on hunger and satiety. Antihistamine inhibits mesenteric lymphatic vessels' endothelium derived relaxing factor (EDRF) causing an increased resistance to lymphatic flow (Nizamutdinova et al. 2014) (Nizamutdinova et al. 2017). Accumulation of mesenteric lipids ensues, with increased abdominal subcutaneous fat, intracapsular brown fat, weight gain, high fasting blood glucose and triglycerides. Mice treated with desloratadine exhibited increased lymphatic tone and resistance with similar fat, weight and biochemical changes (Gasheva et al. 2019). Local changes within the abdominal lymphatics and lipids may explain increase in sensation of physical fullness in our patients that is associated with higher weight gain during the first half of the study. Animal studies showed that mice given antihistamine had increased food intakes and weight gain (Mercer et al. 1994) (Jørgensen et al. 2007). A meta-analysis showed antihistamines induced weight gain in adult asthma patients (E Van Ganse et al. 1997). The NHANES showed antihistamine users had higher WC and insulin levels alongside higher weight (Ratliff et al. 2010). However, there were no differences in fasting blood glucose and lipid levels compared to healthy controls. Obesity is closely related with MetS. We did not find significant increases in WC, BP, blood sugar and lipid levels. However, three patients developed MetS at week 12 which may suggest an effect of loratadine but we feel that our study duration was too short to properly assess development of MetS.

LORATADINE EFFICACY AND SAFETY

Loratadine has good efficacy and safety profile compared to first generation antihistamine in reducing CSU symptoms and improving patients' quality of life (Sharma et al. 2014). Loratadine is comparable to cetirizine and newer antihistamine such desloratadine (Sharma et al. 2014). Our loratadine efficacy results were as expected and side effects were mild and did not lead to discontinuation of treatment. The side effects were not associated with antihistamine dose.

LIMITATIONS

The COVID-19 pandemic affected recruitment of patients into the study despite our efforts to recruit from 2 study sites. The pandemic caused some patients to withdraw from the study due to risk of infection from the hospital. Unfortunately, the study period coincided with the fasting month of Ramadhan for 18 Muslim patients. Eleven patients had experienced weight reduction which typically occurs during the fasting month. Eid celebrations may cause weight gain. However, although the study is under-powered and transient weight loss was observed in a few Muslims, weight gain was still statistically significant. Our results did show an association between anti-histamine and

weight gain is in accordance with the large population data base study (Ratliff et al. 2010). Other possible confounding factors that affect weight which were not assessed were calorie intake and expenditure. The movement control order may cause lifestyle to be more sedentary.

CONCLUSION

Loratadine may have induced weight gain in patients with CSU. A few patients developed MetS. These side effects should be monitored in patients on prolonged loratadine therapy as weight gain may not be associated with perceptible appetite changes.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health, Malaysia for granting the use of the Ministry of Health facilities for the conduct of this research and kind permission to publish this manuscript.

FUNDING

No funding was received for this study.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ETHICAL APPROVAL

Ethical approvals were obtained from the Research Ethics Committee board of National University of Malaysia (FF-2020-797) and the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-20-2744-57481).

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