THE ASSOCIATION BETWEEN OVERWEIGHT/OBESITY
AND CHRONIC SPONTANEOUS URTICARIA

BY

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Abstract

Chronic spontaneous urticaria (CSU) is marked by the appearance of transient pruritic wheals, sometimes accompanied by angioedema, without eliciting factors, and lasting over six weeks. The link between overweight/obesity and CSU remains underexplored. This study aimed to investigate the relationship between overweight/obesity and CSU. Conducted as a retrospective case-control study, this research assessed patients aged 18 and above, documented in the electronic medical records at the outpatient department of the Institute of Dermatology in Thailand from 2018 to 2020. The study included 382 CSU patients and 382 non-CSU controls who were categorized based on Body Mass Index (BMI) into two groups: BMI < 23 (reference group) and BMI $\geq$ 23 (indicating overweight/obesity). Logistic regression analysis revealed no significant association between overweight/obesity and CSU (Odds ratio = 1.03, 95% confidence interval 0.78-1.37, p-value = 0.828). Notably, an elevated Erythrocyte Sedimentation Rate (ESR) was significantly associated with the BMI $\geq$ 23 group (p-value = 0.036), which supported CSU and overweight/obesity that may be linked in a pathogenetic involvement in the inflammatory process. Despite these findings, no significant association was established between overweight/obesity and CSU in the Thai adult population, diverging from several previous studies but aligning with some past studies. Further study is essential to validate these findings and explore the potential relationship between overweight/obesity and CSU.

(Total 65 pages)

Keywords: Association, Overweight, Obesity, Chronic Spontaneous Urticaria

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Chapter 1

Introduction

1.1 Background and Significance of the Problem

Urticaria is a heterogeneous group of diseases characterized by wheals and flares that sometimes concomitantly present with angioedema (Kulthanan et al., 2016). If the symptoms persist for more than six weeks, it is defined as chronic urticaria (CU). It is divided into two groups based on the role of definite triggers: a) chronic inducible urticaria (CIU), which has specific triggers for developing symptoms, and b) chronic spontaneous urticaria (CSU), which has no definite triggers (Kulthanan et al., 2016; Zuberbier et al., 2022). In the revised guidelines of the International EAACI/GA2LEN/ EuroGuiDerm/ APAAACI, CSU is categorized as type I, associated with autoallergic reactions involving immunoglobulin E (IgE) targeting self-antigens, and type IIb, characterized by autoimmune mechanisms involving mast cell activating autoantibodies (Oztop, Beyaz & Orcen, 2022; Zuberbier et al., 2022).

CSU is the most common type of CU, with an estimated prevalence of 0.5-1% in the overall population. It is observed to be twice as prevalent in women compared to men. The peak occurrence of CSU typically falls within the age range of 20-40 years, with an average duration lasting between 3-5 years (Moestrup, Ghazanfar & Thomsen, 2017), although the pathogenesis of CSU remains unclear. However, the immune system (Autoimmunity), inflammation (Inflammation), blood clotting (Coagulation), and self-allergy (Autoallergy) may be involved (Matano et al., 2020). Mast cells were found to be responsible for the disease, and clinical manifestations were caused by several factors, from which mast cells are released, stimulated, and broken down. It was found that the number of mast cells tripled in patients with CSU, both showing skin rash and without skin area (Bansal & Bansal, 2019).

Obesity is chronic, systemic, and rarely asymptomatic and is an inflammatory process that causes a decrease in immunity to antigens (Zbiciak-Nylec et al., 2018). Therefore, it increases the risk of allergies and other immune-related diseases. It is also a most common element of metabolic syndromes, including abdominal obesity, abnormal fat in the blood, high blood pressure, and high blood sugar levels. In addition, it has been linked to inflammatory processes that increase risk factors for atherosclerosis and coronary heart disease (Chung, Wang, Tsai, Lin, & Chen, 2016; Engin, 2017). The prevalence of obesity has been increasing worldwide and has been a significant health issue associated with disability and mortality (Goda & Masuyama, 2016). In Thailand, the occurrence of overweight (BMI 23 – 24.9 kg/m^2) and obesity (BMI $\geq$25 kg/m^2) in adults was documented at 17.5% and 35% in 2009, respectively (Aekplakorn et al., 2014). Furthermore, this trend has been observed to be on the rise in both male and female populations. According to the Thai National Health Examination Surveys V (NHES V) in 2014, the prevalence of obesity (BMI $\geq$25 kg/m2) stood at 37.5%, 32.9%, and 41.8% overall, as well as among males and females, respectively (Sakboonyarat et al., 2020).

Some studies have indicated that CSU, particularly when it continues for a prolonged period, could be connected to excess weight and obesity. Additionally, a higher body mass has also been associated with the delayed appearance of symptoms of urticaria (Zbiciak-Nylec et al., 2018). Increased body weight has been identified as a significant risk factor in the development of allergic conditions such as CSU and overweight or obesity. There may be a pathogenetic involvement in the inflammatory process (Zbiciak-Nylec et al., 2018; Matano et al., 2020), but there are limited data supports the association between both diseases.

Despite the growing body of research on the association between overweight/obesity and CSU, there has been no investigation conducted in Thailand to date. Therefore, this study aimed to explore the relationship between overweight/obesity and CSU in Thai patients using non-CSU patients as a control group.

1.2 Research Objectives

To study the relationship between overweight/obesity and chronic spontaneous urticaria in Thai patients.

1.3 Research Questions

1.3.1 Is chronic spontaneous urticaria more prevalent in overweight or obese Thai patients?

1.3.2 Is there a correlation between overweight/obesity and chronic spontaneous urticaria in Thai patients?

1.4 Definition of Terms

Overweight is a patient with a body mass index (BMI) of $23 - 24.9$ kg/m^2.

Obesity is a patient with a body mass index (BMI) ≥ 25 kg/m^2.

Chronic Spontaneous Urticaria (CSU) is characterized by wheals and flares that sometimes concomitantly present with angioedema with no definite triggers and symptoms persist for more than six weeks.

Chapter 2

Literature Review

2.1 Urticaria

2.1.1 Definition of Urticaria

Urticaria, commonly known as hives, is an inflammatory skin condition marked by the sudden appearance of smooth, red, or whitening itchy swellings called wheals or hives. These wheals vary greatly in size and shape and typically clear up within 24 hours, returning the skin to its usual appearance. Urticaria can also present with angioedema, which involves deeper skin swelling, sometimes accompanied by pain rather than itchiness, frequently affecting the mucous membranes, and usually subsiding within up to 72 hours—longer than the duration for wheals (Zuberbier et al., 2022; Schettini, Corazza, Schenetti, Pacetti, & Borghi, 2023).

2.1.2 Classification of Urticaria

Urticaria is generally classified into two main categories based on symptom duration: acute urticaria (AU) and chronic urticaria (CU) (Zuberbier et al., 2023). AU episodes last fewer than six weeks, while CU persists for six weeks or more (Coelho, Neto, Bordalo, & Jacob, 2022). CU is further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) (Schettini et al., 2023) as shown in Table 2.1. CSU occurs without any clear external trigger, whereas CIndU is triggered by specific external stimuli (Fukunaga et al., 2023). CIndU includes various subtypes, such as cholinergic urticaria, which is linked to sweating and can cause symptoms like itching and painful papular wheals. The classification of urticaria takes into account not only the duration and triggers but also the presence of wheals and angioedema, which are characteristic signs of the condition (Kolkhir et al., 2022).

Differentiating between these types is essential for effective management and treatment, as it helps in selecting appropriate therapeutic approaches (Maurer, Zuberbier, & Metz, 2022).

Table 2.1 Classification of Urticaria

Type	Subtype	Definition/Triggers
Spontaneous Urticaria	Acute spontaneous urticaria	Spontaneously occur (< 6 weeks)
	Chronic spontaneous urticaria	Spontaneously occur (≥ 6 weeks)
Inducible Urticaria (Physical Urticaria)	Cold urticaria	Cold objects, air, fluids, wind
	Delayed pressure urticaria	Vertical pressure
	Symptomatic dermographism	Mechanical shearing forces
	Vibratory angioedema	Vibratory forces
	Aquagenic urticaria	Water
	Cholinergic urticaria	Increasing core body temperature
	Contact urticaria	Contact with substance

Source: Zuberbier et al., 2022

2.1.2.1 Acute Urticaria

Acute urticaria (AU) is a complex condition marked by the abrupt emergence of wheals, angioedema, or both, influenced by diverse etiological factors. Research has pinpointed infections and medications as common precipitants, with infections being predominant in children under two years old, and medications such as non-steroidal anti-inflammatory drugs being prevalent among adults (Melikoglu, Pala, & Bayraktar, 2022). Additionally, food, insect bites, and idiopathic causes, where no clear cause is discernible, can also initiate the condition (Santa et al., 2022). The pathogenesis of AU involves mast cell degranulation, which results in the release of mediators responsible for the symptoms observed. This process may be initiated by both immunological and non-immunological factors, underscoring the complexity of

the disease's underlying mechanisms (Salman, Porras, & Gimenez-Arnau, 2023). Recent studies have highlighted the role of cytokines and α-defensins in the pathogenesis, pointing to a significant immunoinflammatory component in patients experiencing severe manifestations of the disease (Banadyha & Nakonechna, 2022). Diagnosis is primarily clinical, but laboratory tests can aid in identifying specific underlying causes, such as elevated C-reactive protein levels or particular infections. Routine laboratory testing is not universally recommended, except in cases suspecting an allergic origin, where specific allergy testing may be conducted (Ensina, Min, Félix, de Alcântara, & Costa, 2022). Management of acute urticaria typically involves second-generation antihistamines as the first-line treatment, with systemic corticosteroids reserved for more severe cases (Zaikov, Bogomolov, Kyrylenko, & Gryshylo, 2022). Identifying and avoiding potential triggers is key to preventing recurrence. Despite effective treatments, AU can considerably affect the quality of life, emphasizing the necessity for prompt diagnosis and effective management.

2.1.2.2 Spontaneous Urticaria

1) Acute Spontaneous Urticaria

Acute spontaneous urticaria (ASU) is a condition distinct from CSU, characterized by the sudden appearance of hives, angioedema, or both, lasting for less than 6 weeks. While the provided contexts primarily focus on CSU, insights into the pathophysiology, treatment, and patient experiences of CSU can offer a foundational understanding applicable to ASU, given the shared symptomatology and underlying mechanisms of mast cell activation, albeit with a shorter duration in ASU (Yosipovitch, Biazus Soares, & Mahmoud, 2023).

2) Chronic Spontaneous Urticaria

CSU is a complex condition driven primarily by mast cell activation, characterized by the spontaneous emergence of wheals and angioedema persisting for over six weeks without external provocations (Yosipovitch et al., 2023).

This disorder not only inflicts significant physical discomfort but also imposes profound emotional and economic impacts, complicating the patient's interactions with the healthcare system (Hsieh & Lee, 2017). It is estimated that CSU affects approximately 1% of the population, marking it as a frequent issue in primary and emergency care settings. The etiology of CSU is predominantly autoimmune, involving Type I reactions where IgE antibodies target self-antigens such as thyroid peroxidase and IL-24, and Type IIb reactions characterized by autoantibodies that stimulate mast cells directly (Termeer et al., 2015). The clinical manifestation of CSU is typically a fluctuating course of pruritic wheal and flare lesions that resolve within 24 hours without leaving scars, with about 30%-50% of cases presenting concurrently with angioedema (Armstrong, Soong, & Bernstein, 2023). This unpredictable and severe symptomatology can severely degrade quality of life, highlighting the importance of effective management strategies to alleviate patient suffering.

2.1.2.3 Inducible Urticaria (Physical Urticaria)

Chronic inducible urticaria (CIndU) is characterized by the presence of pruritic wheals and/or angioedema triggered by specific, identifiable stimuli, which contrasts with CSU where such triggers are absent (Mizuno et al., 2022). The pathogenesis of CIndU involves the activation and degranulation of mast cells in the skin, resulting in the release of histamine, a crucial mediator in symptom development (Kulthanan et al., 2022). Despite histamine's central role, the correlation between histamine levels and symptom severity is intricate, and H1-antihistamines often demonstrate variable clinical effectiveness (Moñino-Romero et al., 2023). Studies indicate that basophils in CIndU patients show heightened activation compared to healthy controls, yet their response to anti-IgE or anti-FcεRI antibody stimulation remains comparable to that in healthy individuals and exceeds that in CSU patients (Giménez-Arnau et al., 2022). This suggests that basophils are somewhat activated in CIndU but do not exhibit significant abnormalities in responsiveness (Fukunaga et al., 2023). Additionally, the expression of IgE and the high-affinity IgE receptor (FcεRI) on basophils appears normal in CIndU patients (Grieco et al., 2022), pointing to potential mechanisms in the pathophysiology of CIndU beyond simple IgE-FcεRI

interactions. Management of CIndU, particularly in antihistamine-resistant subtypes, can be challenging. Omalizumab, an anti-IgE antibody, has been effective across various CIndU subtypes, including symptomatic dermographism, cold urticaria, and solar urticaria, offering rapid symptom relief and improved quality of life (Kolkhir et al., 2022). This underscores the significance of IgE in the pathogenesis of CIndU and advocates for the use of targeted therapies (Maurer et al., 2018). The identification of emerging subtypes, such as follicular traction urticaria, highlights the diversity of triggers and the necessity for continued research to elucidate underlying mechanisms and develop efficacious treatments (Raison-Peyron, Reymann, & Bessis, 2017). Furthermore, the potential involvement of the extrinsic coagulation cascade and complement factors in urticaria pathogenesis suggests new avenues for therapeutic intervention (Yanase, Takahagi, Ozawa, & Hide, 2021).

1) Cold Urticaria

Cold urticaria is marked by the onset of urticaria following exposure to cold temperatures. This condition can manifest in either an acquired or familial form, with the acquired type being more prevalent and typically idiopathic, meaning its cause remains unidentified. Acquired cold urticaria (ACU) is diagnosed through patient history and positive results from the cold stimulation time test (CSTT) and can occasionally be precipitated by factors such as medication intake (Gandhi, Healy, Wanderer, & Hoffman, 2009). In contrast, familial forms like familial atypical cold urticaria (FACU) and familial cold urticaria (FCU) exhibit autosomal dominant inheritance patterns. FACU is differentiated from ACU by its clinical course, triggers, the severity of systemic reactions, and negative CSTT results (Hoffman, Wright, Broide, Wanderer, & Kolodner, 2000). FCU is characterized by intermittent episodes of rash accompanied by fever, arthralgias, and leukocytosis following general exposure to cold, with some cases progressing to late-onset reactive renal amyloidosis (Kränke & Mayr-Kanhäuser, 2002). The underlying pathogenesis of cold urticaria involves the degranulation of mast cells upon exposure to cold, resulting in the release of histamine and other mediators that provoke symptoms (Ombrello et al., 2012). In some instances, cold urticaria has been associated with the presence of IgG

autoantibodies against the high-affinity IgE receptor (FcεRIα), which may activate mast cells and basophils, leading to whealing and angioedema (Martens & Berrens 1975). Therapeutic approaches for managing cold urticaria include avoiding cold exposure, using antihistamines, and in severe instances, employing treatments like omalizumab, which have shown effectiveness (Greaves & O'Donnell, 1998). Recent studies have investigated the role of the transient receptor potential ankyrin 1 (TRPA1) channel in mediating noxious cold perception through the transduction of reactive oxygen species (ROS) signaling, offering insights into a possible molecular mechanism responsible for cold-induced pain in this condition (Cunha et al., 2017).

2) Delayed Pressure Urticaria

Delayed Pressure Urticaria (DPU) is a specialized subtype of CU marked by the development of deep dermal wheals following sustained pressure, typically manifesting 1–12 hours post-application. A study among Japanese patients identified a 3.1% prevalence rate for DPU within the broader context of chronic urticaria, noting its distinct resistance to antihistamines and subsequent reliance on steroids for management. Notably, eosinophil infiltration in skin biopsies highlights the inflammatory basis of DPU (Morioke et al., 2010). This involvement of eosinophils is also evident in a case of exercise-induced joint effusion featuring synovial fluid eosinophilia in a DPU patient, pointing to a multifaceted interaction between mast cells, eosinophils, and potential local complement activation in the inflammation associated with DPU (Miossec, Sullivan, Tharp, Volant, & Le Goff, 1987). The occurrence of delayed reactions is prevalent in various contexts beyond DPU, such as drug hypersensitivity and vaccine-induced urticaria. Delayed urticaria following COVID-19 vaccination, emerging several days after inoculation, suggests an immunological basis for such delayed responses (Bianchi et al., 2022). Similarly, bupropion-induced urticaria in individuals with depressive disorders showcases a type of drug-related delayed urticaria, with a notable increase in urticaria cases within the first four weeks of treatment, particularly between days 15–28 (Hu et al., 2013). Moreover, the spectrum of delayed urticarial responses, including delayed cold urticaria and drug hypersensitivity reactions, illustrates their diversity and clinical

significance, which can range from benign skin manifestations to severe cutaneous adverse reactions (SCARs). These phenomena underscore the necessity for comprehensive diagnostic approaches like patch testing and intradermal testing, and possibly the exploration of genetic markers to enhance understanding and management of delayed hypersensitivity reactions (Bäck & Larsen, 1978; Copaescu, Gibson, Li, Trubiano, & Phillips, 2021).

3) Symptomatic Dermographism

Symptomatic dermographism (SD) is recognized as the most common type of CIndU, characterized by the development of wheals following mechanical irritation of the skin (Yang, Kong, Wang, Song, & Chen, 2023). This condition significantly affects patients' quality of life, underscoring the need for efficient diagnostic and therapeutic strategies (Rujitharanawong et al., 2022). Notable triggers include medications such as minocycline, which has been linked to the induction of SD in patients treated for acne vulgaris or rosacea (Drivenes, Banerji, & Bygum, 2022). The epidemiology and clinical manifestations of SD show a higher prevalence in tropical regions and a greater incidence among females compared to males. Risk factors such as older age, increased body weight, and certain comorbid conditions have been correlated with a higher likelihood of developing SD. Diagnostic procedures predominantly rely on provocation testing, utilizing instruments like the dermographometer and skin writometer to measure disease activity and determine provocation thresholds. Intriguingly, food intake has emerged as a potential cofactor influencing the results of provocation tests, indicating the existence of SD subtypes that are exacerbated or triggered by dietary factors (Yücel et al., 2022). Therapeutically, antihistamines represent the primary treatment modality, with omalizumab, an anti-IgE monoclonal antibody, providing significant improvements in disease management and quality of life for patients who do not respond to antihistamines.

4) Vibratory Angioedema

Vibratory angioedema is a rare variant of physical urticaria, characterized by transient reactions induced by vibratory stimuli. This condition may manifest as either hereditary or acquired, with some instances linked to specific genetic mutations (Vergara-de-la-Campa et al., 2020; Gatica-Ortega, Sánchez-Matas, Sánchez-Muñoz, & Pastor-Nieto, 2022). Clinically, it presents with symptoms of angioedema such as swelling of the tongue, palate, and throat, which can be triggered by actions involving vibratory forces, such as playing musical instruments or operating pneumatic tools (Kalathoor, 2015; Zhao, Reimann, Wang, Wang, & Zuberbier, 2019). The treatment of vibratory angioedema poses distinct challenges, as some cases show resistance to conventional therapies like antihistamines and corticosteroids. However, there have been positive responses to treatments such as amitriptyline and bromazepam, which points to a possible neuroinflammatory mechanism underlying its pathogenesis (Guarneri, Guarneri, & Marini, 2014). Accurate diagnosis is essential to distinguish vibratory angioedema from other similar conditions, such as delayed pressure urticaria.

5) Aquagenic Urticaria

Aquagenic urticaria is an uncommon type of physical urticaria distinguished by the emergence of wheals and pruritus upon contact with water, regardless of its temperature or chemical composition. This condition is characterized by the appearance of 1-2mm folliculopapular urticarial papules approximately 20-30 minutes after water exposure, typically resolving within 30-60 minutes after drying. The etiology of aquagenic urticaria is not fully understood, with proposed mechanisms including both histamine-mediated and histamine-independent pathways (Jaabouti, Benchidmi, Hafidi, Bencchakroun, & Mahraoui, 2023). The diagnosis predominantly relies on the patient's clinical history and is substantiated through water provocation tests, which are regarded as the definitive diagnostic method (Baudy, Bessis, & Raison-Peyron, 2022). Treatment strategies include the use of second-generation antihistamines as the primary approach, supplemented by ultraviolet monotherapy,

topical barrier creams, and acetylcholine antagonists (Fukayama, Domoto, Sato, & Asano, 2021). In cases resistant to these treatments, omalizumab has demonstrated efficacy (Robles-Tenorio, Tarango-Martinez & Sierra-Silva, 2020; Carra, Dereure, & Raison-Peyron, 2022). The symptoms of aquagenic urticaria can significantly diminish the quality of life, leading to daily discomfort (Legat, 2023). Additionally, aquagenic urticaria has been linked with other cutaneous disorders such as acquired aquagenic keratoderma (AAK), and some patients present concurrently with both AU and AAK (Prashamsa, Null, & Rm 2020). Aquagenic pruritus, a related condition characterized by intense itching upon contact with water without visible lesions, further extends the spectrum of water-induced dermatological reactions (Ercan, Ozmen, & Bostanci, 2019).

6) Cholinergic Urticaria

Cholinergic urticaria is a specialized type of physical urticaria that is activated by an increase in body core temperature, typically due to activities like exercise, bathing, or emotional stress, which results in the formation of small, pruritic wheals surrounded by erythema (Kumaran, Arora, & Parsad, 2017). Although cholinergic urticaria has been recognized for many years, its epidemiology and clinical features are not fully understood, with studies documenting a range of clinical manifestations and varied responses to treatment. The pathogenesis of cholinergic urticaria is intricate and not completely resolved, involving diverse mechanisms such as the release of acetylcholine, allergy to sweat, superficial blockage of sweat ducts, and acquired generalized hypohidrosis, among others (Fukunaga et al., 2018). Cholinergic urticaria can be classified into subtypes based on its underlying mechanisms, including cholinergic urticaria with poral occlusion, cholinergic urticaria with acquired generalized hypohidrosis, cholinergic urticaria with sweat allergy, and idiopathic cholinergic urticaria. This classification highlights the condition's heterogeneity and indicates that a customized approach to management is essential (Fukunaga et al., 2023). Diagnosis and treatment necessitate careful consideration of its subtypes and may include the use of antihistamines, anticholinergic agents, and, in cases resistant to standard treatments, therapies such as omalizumab. The involvement

of acetylcholine in the onset of cholinergic urticaria symptoms has been recognized, with severe cases occasionally responding to anticholinergic therapy when traditional methods are ineffective. Recent research has also pointed out the importance of evaluating sweating abnormalities when examining patients with cholinergic urticaria, proposing that a thorough assessment of sweat function could improve management outcomes (Nakamizo, Egawa, Miyachi, & Kabashima, 2012).

7) Contact Urticaria

Contact urticaria is characterized by a wheal, itching, and flare reaction that manifests upon exposure to an allergen. The pathogenesis of contact urticaria is diverse, comprising non-immunological, immunological, and undetermined causes (Bhatia, Alikhan, & Maibach, 2009). In cases of immunological contact urticaria, the reaction is a hypersensitivity response initiated by direct contact with a specific allergenic substance (Tuer, James, & Summers, 1986). Diagnostic approaches for contact urticaria include various tests such as the prick test and the guinea pig ear model, which help identify the causative agents and differentiate between immunological and non-immunological types (Maibach & Johnson, 1975). Treatment strategies for contact urticaria have evolved, with specific immunotherapy and anti-IgE monoclonal antibodies proving particularly effective in managing cases with complex etiologies. Immediate reactions to a range of substances, including preservatives, further underscore the broad spectrum of triggers associated with this condition.

2.1.3 Mechanisms and Pathophysiology of Urticaria

The pathophysiology of urticaria, particularly chronic spontaneous urticaria (CSU), encompasses intricate interactions among immune cells, inflammatory mediators, and various biological systems. Central to the pathogenesis of CSU is the activation of mast cells and basophils, which release histamine and other vasoactive substances, resulting in the characteristic wheals and angioedema observed in patients (Zhou, Li, Liu, Zhu, & Peng, 2022; Tomaszewska, Słodka, Tarkowski, & Zalewska-

Janowska, 2023; Yanase et al., 2023). These cells may be triggered by autoimmune mechanisms, including the production of autoantibodies against the high-affinity immunoglobulin E (IgE) receptor (FcεRI) or IgE itself, mechanisms implicated in a substantial portion of chronic idiopathic urticaria cases (Yanase et al., 2021). Emerging research also highlights the potential role of the gut microbiota in influencing CSU's pathogenesis, suggesting that alterations in gut microbiota composition and serum metabolites could affect immune and inflammatory pathways (Luo et al., 2023). Additionally, the extrinsic coagulation cascade and complement system have been recognized as contributors to the disease process, with tissue factor (TF)-triggered coagulation and complement components like C3a and C5a playing roles in mast cell and basophil activation (Murdaca, Paladin, Borro, Ricciardi, & Gangemi, 2023). The neuro-immuno-psychological dimensions of CSU underscore the impact of psychological stress on triggering or exacerbating the condition, mediated through a diverse array of inflammatory mediators, neuropeptides, and neurotransmitters (Fukunaga et al., 2023). Furthermore, the classification of urticaria into autoallergic and autoimmune subtypes is supported by transcriptomic analyses that reveal differential gene expression and pathway activation related to Th2 and Th17 cells in lesional skin, which correlates with disease severity (Ring, 2016).

2.1.4 Diagnosis of Urticaria

2.1.4.1 Acute Urticaria

Acute urticaria is a condition that typically resolves on its own and typically does not necessitate the use of routine or extensive diagnostic evaluations unless strongly indicated by the patient's medical background. For instance, individuals with a history of type I food allergies or drug hypersensitivity may experience urticaria symptoms shortly after being exposed to the corresponding allergens, and allergy tests could be beneficial in preventing future encounters with causative agents (Kolkhir et al., 2022).

2.1.4.2 Chronic Spontaneous Urticaria

In every individual with CSU, the diagnostic evaluation consists of a comprehensive patient history, physical examination, standard laboratory tests, and the evaluation of disease severity, impact, and management. The standard tests involve a complete blood count, C-reactive protein (CRP), and/or erythrocyte sedimentation rate (ESR) for all patients, as well as total immunoglobulin E (IgE) and anti-thyroid peroxidase antibodies (anti-TPO) for patients under specialized medical supervision. Based on the findings from these assessments, additional diagnostic investigations may be conducted as deemed necessary (Zuberbier et al., 2022).

The 7C concept, as outlined in the current international guideline for urticaria, presents the seven objectives of the diagnostic evaluation for individuals with CSU. The 7C concept as shown in Table 2.2, comprises of confirm, cause, cofactors, comorbidities, consequences, components, and course (Kolkhir et al., 2022; Zuberbier et al., 2022).

Table 2.2 The Objective of Diagnostic Evaluation for CSU Patients

7C Concept	History/Physical Examination/ Basic Tests
Confirm	Rule out differential diagnosis
Cause	Search for indicators of CSU[aiTI], CSU[aiTIIb]
Cofactors	Search for triggers and aggravators
Comorbidities	Look for signs of autoimmunity, mental health
Consequences	Identify issues related to sleep, distress, sexual health, work, social performance
Components	Evaluate potential biomarkers/ predictors of treatment response
Course	Monitor CSU activity, impact, and control

Source: Zuberbier et al., 2022

2.1.4.3 Chronic Inducible Urticaria

The goal of diagnostics in CIndU is to rule out other potential diagnoses, pinpoint the specific subtype of CIndU, and establish the thresholds that trigger symptoms. The identification of trigger thresholds is crucial for evaluating disease activity and monitoring treatment effectiveness. Various validated tools for provocation testing are typically accessible for most subtypes of CIndU, as shown in Table 2.3. (Zuberbier et al., 2022)

Table 2.3 Recommended Diagnostic Tests in Frequent Urticaria Subtype

Type	Subtype	Routine Diagnostic Tests
Spontaneous Urticaria	Acute spontaneous urticaria	None
	Chronic spontaneous urticaria	Differential blood count. ESR and/or CRP, IgG anti-TPO & total IgE
Inducible Urticaria (Physical Urticaria)	Cold urticaria	Cold provocation & threshold test
	Delayed pressure urticaria	Pressure test & threshold test
	Heat urticaria	Heat provocation & threshold test
	Solar urticaria	UV & visible light & threshold test
	Symptomatic dermographism	Elicit dermographism & threshold test
	Vibratory angioedema	Test with vibration
	Aquagenic urticaria	Provocation testing
	Cholinergic urticaria	Provocation & threshold testing
	Contact urticaria	Provocation testing

Source: Zuberbier et al., 2022

2.1.5 Management of Patients with Urticaria

The management and treatment of urticaria are critical aspects of dermatological care, aiming to alleviate symptoms, prevent recurrence, and improve patients' quality of life. The strategies vary depending on the type of urticaria (acute or chronic) and may involve a combination of lifestyle modifications, pharmacological treatments, and in some cases, novel therapies.

2.1.5.1 General Management

General management of urticaria focuses on identifying and avoiding triggers, which can vary widely among individuals. Common triggers include certain foods, medications (like NSAIDs and ACE inhibitors), physical stimuli (such as pressure, and temperature changes), and stress. For many patients, keeping a symptom diary can be useful in identifying potential triggers. Educating patients about the nature of the disease and possible trigger avoidance is a cornerstone of managing urticaria.(Ryan et al., 2022)

2.1.5.2 Pharmacological Treatments

Pharmacotherapy is typically tiered based on the severity and frequency of symptoms as shown in Figure 2.1.

First-line Therapy: The first line of treatment usually involves non-sedating H1 antihistamines, such as cetirizine, fexofenadine, or loratadine. These drugs are preferred due to their efficacy in reducing itch and hives and their favorable side effect profile compared to first-generation antihistamines, which cause sedation. For many patients, these may be taken on a regular basis rather than on an as-needed basis to prevent symptoms (Yosipovitch et al., 2023).

Increased Doses of H1 Antihistamines: If symptoms persist despite regular use of a standard dose, guidelines recommend increasing the dose up to

fourfold. High-dose H1 antihistamines have been found effective and safe for many patients and can significantly improve quality of life (Hong, Weng, Ye, & Liu, 2023).

Addition of Other Agents: If symptoms continue to be uncontrolled, other agents like H2 antihistamines (e.g., ranitidine), leukotriene receptor antagonists (e.g., montelukast), or a short course of oral corticosteroids may be considered. However, long-term use of corticosteroids is generally avoided due to significant side effects (Khan, 2013).

Omalizumab: For CSU that does not respond to antihistamines, omalizumab, an anti-IgE monoclonal antibody, has been approved and shown to be highly effective. Omalizumab works by blocking the interaction of IgE with its receptors on mast cells and basophils, thereby reducing the release of histamine and other mediators of inflammation (Wedi & Traidl, 2021).

Cyclosporine: In severe cases of urticaria, immunosuppressants like cyclosporine have been used effectively. However, due to potential side effects, its use is typically reserved for cases that do not respond to other treatments and is carefully monitored (LaCava & Fadugba, 2023).

2.1.5.3 Emerging Therapies

Research is ongoing into new treatments for urticaria. Potential new drugs include other biologics targeting different parts of the immune response implicated in urticaria, such as ligelizumab, another anti-IgE antibody that has shown promise in clinical trials (Kolkhir, Altrichter, Munoz, Hawro, & Maurer, 2020).

2.1.5.4 Treatment of Special Populations

Special considerations are necessary when treating populations like pregnant women, children, and the elderly. For example, in pregnant women, certain

medications may be contraindicated due to potential risks to the fetus. Children may require different dosing guidelines, and the elderly might be more sensitive to side effects of medications (Antia, Baquerizo, Korman, Alikhan, & Bernstein, 2018).
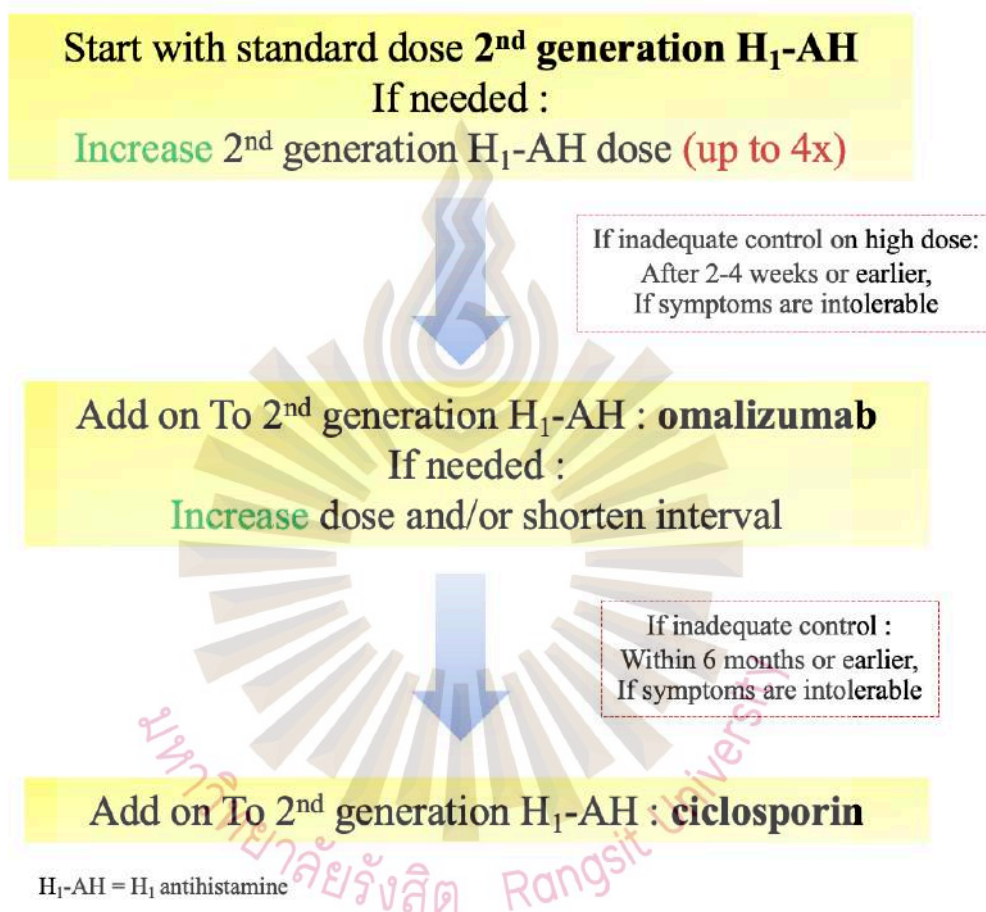
Figure 2.1 Recommended Treatment Algorithm for Urticaria

Source: Zuberbier et al., 2022

2.1.5.5 Complementary and Alternative Medicine (CAM)

Some patients turn to CAM therapies such as herbal supplements, acupuncture, or dietary changes. While evidence is less robust for these treatments, they may offer additional relief for some patients and are typically considered when conventional therapies fail or as adjuncts to medical treatment (Shi et al., 2022).

2.2 Obesity/Overweight

2.2.1 Definition of Obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. The most widely used method to classify overweight and obesity in adults is the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters (kg/m²). Obesity has emerged as a significant global public health challenge, not only because of its widespread prevalence but also due to its association with a range of chronic diseases. The World Health Organization (WHO) has consistently highlighted obesity as a critical issue, noting a dramatic increase in global rates over the past few decades (WHO, 2020).

2.2.2 Epidemiology of Obesity

2.2.2.1 Global Trends

The global obesity epidemic is characterized by its widespread prevalence across both genders and all age groups, but there are notable variations by region, socioeconomic status, and age. According to the World Health Organization (WHO), the prevalence of obesity nearly tripled worldwide between 1975 and 2016 (WHO, 2020). In 2016, over 39% of adults aged 18 years and older were overweight, and 13% were obese, with higher rates observed in more affluent countries (WHO, 2020).

2.2.2.2 Regional Variations

North America: The United States has one of the highest obesity rates globally, with more than one-third of the adult population classified as obese (Hales, Carroll, Fryar, & Ogden, 2020). The prevalence of obesity is notably higher among middle-aged adults and non-Hispanic black populations.

Europe: Obesity rates vary significantly across Europe, with higher prevalence in Eastern and Southern Europe. Countries like the UK and Hungary report higher obesity rates compared to countries like Italy and France (OECD, 2019).

Asia: Asian countries traditionally had lower obesity rates, but recent urbanization and economic development have led to a rise in obesity, especially in urban areas. For example, China and India are experiencing rapid increases in obesity rates among all age groups (Popkin & Slining, 2013).

Africa: Obesity is on the rise in Africa, particularly in urban settings. South Africa has some of the highest rates on the continent, driven by a shift towards more sedentary lifestyles and increased consumption of processed foods (Agyemang et al., 2016).

2.2.3 Etiology of Obesity

The etiology of obesity is complex and multi-faceted, driven by genetic, environmental, psychological, and physiological factors. Genetic predispositions, such as those linked to the FTO gene, play a critical role in an individual's risk for obesity by influencing appetite and metabolism (Frayling et al., 2007). However, the dramatic increase in obesity rates also implicates significant environmental contributions, characterized by the 'obesogenic' modern lifestyle that includes a prevalence of high-calorie foods and sedentary behaviors (Booth, Roberts, & Laye, 2012; Malik, Willett, & Hu, 2013). Socioeconomic and cultural factors further modulate these risks, with varying impacts on dietary habits and physical activity levels across different demographics (Wang & Lim, 2012). Psychological responses to stress and emotional factors also contribute, as seen in patterns of emotional eating (Konttinen, Haukkala, Sarlio-Lähteenkorva, Silventoinen, & Jousilahti, 2009). Additionally, physiological aspects like individual metabolic rates and hormonal influences such as leptin and insulin resistance play significant roles in the development and persistence of obesity (Levine, Eberhardt, & Jensen, 1999; Myers, Leibel, Seeley, & Schwartz, 2010).

Understanding these interplays is crucial for developing effective interventions against the growing obesity epidemic.

2.2.4 Pathogenesis of Obesity

The pathogenesis of obesity is a complex interaction of physiological, genetic, and environmental factors leading to an energy imbalance and excessive fat accumulation. Central to obesity is the disruption in energy balance regulation, where factors such as basal metabolic rate, influenced by age, sex, and muscle mass (Levine et al., 1999), and the thermic effect of food (Westerterp, 2004), play key roles. Genetics also significantly contribute, with genes like FTO and MC4R affecting appetite and energy regulation (Frayling et al., 2007; Loos, 2018). Environmental influences, particularly modern diets rich in high-calorie foods and a decline in physical activity due to technological advancements, exacerbate these risks (Ng & Popkin, 2012). Additionally, the neuroendocrine system, including hormones like leptin and ghrelin, regulates hunger and satiety (Myers et al., 2010), while psychological stress can lead to emotional eating, further complicating obesity's pathogenesis (Konttinen et al., 2009). Understanding these interrelated mechanisms is crucial for developing effective prevention and treatment strategies for obesity.

2.2.5 Health Risks Associated with Obesity

Obesity significantly elevates the risk for numerous health conditions, impacting nearly every system in the body and potentially reducing life expectancy. It is a principal risk factor for cardiovascular diseases, including heart disease, stroke, and hypertension, primarily due to physiological changes like increased blood pressure and altered cholesterol levels (Poirier et al., 2006). Similarly, obesity is the most significant predictor of type 2 diabetes, linked to about 80-85% of cases due to insulin resistance (American Diabetes Association, 2018). The condition also increases the risk of various cancers, such as endometrial and colon, through mechanisms like inflammation and hormonal imbalances (Lauby-Secretan et al., 2016). Respiratory issues like obstructive sleep apnea are more prevalent in obese individuals, often

exacerbated by excess neck fat which obstructs breathing (Littleton, 2012). Obesity also stresses the musculoskeletal system, heightening the risk of osteoarthritis and joint degeneration (Anandacoomarasamy, Fransen, & March, 2009). Furthermore, it is a critical component of metabolic syndrome, a cluster of symptoms that significantly raise the risk of cardiovascular disease and diabetes (Grundy, 2004). Not limited to physical health, obesity severely affects psychological well-being, leading to conditions like depression and anxiety due to social stigma and self-esteem issues (Luppino et al., 2010). Overall, the severe health implications associated with obesity underline the urgent need for effective public health strategies and individual interventions to manage and mitigate its impacts.

2.2.6 Clinical Interventions for Obesity

Clinical interventions for obesity encompass a variety of strategies aimed at managing and reducing the condition through sustainable weight loss and risk mitigation. These include lifestyle modification programs that focus on dietary adjustments, increased physical activity, and behavioral therapy to support long-term changes. When these adjustments prove insufficient, pharmacotherapy may be employed, using FDA-approved medications like Orlistat, Phentermine-Topiramate, Liraglutide, Bupropion-Naltrexone, and Semaglutide, the latter being highlighted for its effectiveness in a study by Wilding et al. (2021). For severe cases, bariatric surgery options such as Roux-en-Y Gastric Bypass, Sleeve Gastrectomy, and Adjustable Gastric Band are available, which significantly alter the gastrointestinal anatomy to promote weight loss and improve comorbid conditions. Additionally, emerging therapies and combination treatments continue to evolve, offering hope for future advancements in obesity treatment. Together, these approaches provide a comprehensive, tailored strategy involving a multidisciplinary team to effectively manage obesity.

2.2.7 Prevention Strategies for Obesity

Addressing the obesity epidemic requires a multi-layered approach involving individual, community, and policy-level strategies aimed at promoting healthier lifestyles and decreasing obesity prevalence. Public health policies like sugary drinks taxes, which have proven effective in places like Mexico and some U.S. cities, help reduce sugary drink consumption—a major caloric contributor to obesity (Colchero, Popkin, Rivera, & Ng, 2016). Nutritional labeling and urban design that encourages physical activity also play vital roles in supporting healthy choices. Schools and workplaces are pivotal arenas for obesity prevention, implementing programs that educate about nutrition, increase physical activity, and offer healthier meal options. On a clinical level, interventions may include behavioral therapy, pharmacotherapy, and in severe cases, bariatric surgery, which has shown significant long-term benefits for weight loss and diabetes management (Schauer et al., 2017). Community-based initiatives such as farmers' markets, community gardens, and support groups provide localized support and access to healthy options, underscoring the importance of a comprehensive strategy that integrates various sectors to effectively combat obesity.

2.3 The Association between Overweight/Obesity and CSU

Many studies have been conducted to examine the association between overweight/obesity and CSU, as shown in Table 2.4.

Table 2.4 Studies on the Association between Overweight/Obesity and CSU

Authors (year)	Methods	Study Focus	Summary of Findings
Kim, Han, Lee, Lee, & Park (2019)	▪ Long-term retrospective cohort study ▪ n= 289,493 ▪ Nationwide database	▪ BMI and/or waist circumference (WC) + CSU	▪ Higher BMI and WC have a weak association with higher CSU risk. ▪ Abdominal obesity has a more significant effect on CSU risk compared to overall obesity. ▪ Obesity-related systemic inflammation could play a role in the development of CSU.
Shalom et al. (2018)	▪ Cross-sectional study ▪ n=11,261 ▪ Large community-based medical database	▪ Metabolic syndrome (MS) + CU	▪ CU is linked with MS and its components. ▪ CU patients showed higher rates of obesity, diabetes, hyperlipidemia, hypertension, and gout. ▪ It is recommended to screen for MS in CU patients.
Zbiciak-Nylec et al. (2018)	▪ Observational study ▪ n=85 ▪ no control group	▪ Overweight and obesity + CSU	▪ CSU may be linked to overweight & obesity. ▪ CSU, especially if long duration, may be associated with overweight & obesity. ▪ Higher body mass can delay CSU symptoms onset.
Vena & Cassano (2017)	▪ Review article	▪ MS + CSU	▪ Increased MS prevalence observed in patients with uncontrolled CU. ▪ CSU & MS have shared pathomechanisms

Table 2.4 Studies on the Association between Overweight/Obesity and CSU (Cont.)

Authors (year)	Methods	Study Focus	Summary of Findings
Lapi et al. (2016)	▪ Cross-sectional study n=14,859 ▪ Longitudinal patient database	▪ Epidemiology of CSU	▪ Female had higher prevalence and incidence rates than males. ▪ Obesity, anxiety disorders, malignancies, and use of certain drugs were associated with increased risk of CSU.
Choudhary & Shrestha (2020)	▪ Observational study ▪ n=151 ▪ no control group	▪ Obesity + CSU	▪ A high occurrence of urticaria is seen in individuals who are overweight or obese.
Ye et al. (2013)	▪ Cross-sectional study ▪ n=131	▪ MS + CU	▪ Patients with CU & MS displayed elevated urticaria activity scores. ▪ CU & MS exhibit persistent low-level inflammation related to TNF-a, eosinophil cationic protein (ECP), and C3. ▪ Addressing central obesity and dyslipidemia could potentially aid in managing CU.
Matano et al. (2020)	▪ Case-control study ▪ n=? ▪ Diet history questionnaire	▪ Dietary habits + CSU	▪ CSU patients had elevated BMI in comparison to the control group. ▪ CSU is linked to increased BMI & consumption of eggs. ▪ High consumption of beverages, coffee, and caffeine-rich drinks is linked to uncontrolled CSU.

Table 2.4 Studies on the Association between Overweight/Obesity and CSU (Cont.)

Authors (year)	Methods	Study Focus	Summary of Findings
Soria et al. (2018)	▪ Observational study ▪ French national, non-interventional, multicenter ▪ n=278 ▪ no control group	▪ Obesity + CU	▪ Obesity was not associated with severe CU.

Chapter 3

Research Methodology

3.1 Population and Samples

This study was a retrospective case-control study of CSU and those over 18 years old. Demographic data were recorded in the EMR of all patients at the outpatient department of the Institute of Dermatology from 2018-2020 (1 January 2018 to 31 December 2020).

3.1.1 Inclusion Criteria (Case)

1) Patients diagnosed with chronic urticaria who were not previously received treatment at the outpatient department of the Institute of Dermatology (New cases).

2) Age ≥18 years

3.1.2 Exclusion Criteria (Case)

1) Patients with acute urticaria.

2) Patients with urticaria caused by physical factors (inducible urticaria or physical urticaria) such as pressure urticaria, cold urticaria, heat urticaria, dermographism urticaria, cholinergic urticaria, and contact urticaria.

3) During follow-up, the patient was diagnosed with other diseases (non-chronic urticaria) again.

4) Incomplete data, such as age, weight, height, and clinical symptoms, including symptoms and duration of the disease.

3.1.3 Inclusion Criteria (Control)

1) A new patient who receives services at the outpatient department of the Institute of Dermatology (New hospital number) each year with information recorded in the EMR

2) Diagnosis of other diseases (non-chronic urticaria)

3) Age ≥18 years

3.1.4 Exclusion Criteria (Control)

1) Patients in the category of skin diseases and autoimmune skin diseases associated with metabolic syndrome and chronic spontaneous urticaria, e.g., psoriasis, acne vulgaris, hidradenitis suppurativa, androgenetic alopecia, acanthosis nigricans, atopic dermatitis, lichen planus, autoimmune bullous disease, Sjogren syndrome, Bechet's disease, and vasculitis.

2) Incomplete data, including age, weight, height, and diagnosed disease or either.

3.2 Size of Sample

Calculated from Formula (without continuity Correction):

Formula;
$$n = \left[\frac{z_{1-\frac{\alpha}{2}}\sqrt{\overline{pq}\left[1+\frac{1}{r}\right]} + z_{1-\beta}\sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2 \qquad (3\text{-}1)$$

When; p_2* = P(exposure/control) = 0.409, $q_2 = 1 - p_2 = 1 - 0.409 = 0.591$

p_1** = P(exposure/case) = 0.51, $q_1 = 1 - p_1 = 1 - 0.51 = 0.49$

$\overline{p} = \frac{p1 + p2\,r}{1+r} = \frac{(0.51) + [(0.409)(1)]}{1+(1)} = 0.4595$

$\overline{q} = 1 - \overline{p} = 1 - 0.4595 = 0.5045$

$r = \frac{n\,case}{n\,control} = 1$

$$z_1 - \frac{\alpha}{2} = 1.96$$

$$z_1 - \beta = 0.8$$

Therefore, in the following formula:

$$\text{n case} = \left[\frac{(1.96)\sqrt{(0.4595)(0.5045)\left[1+\frac{1}{(1)}\right]} + (0.8)\sqrt{(0.51)(0.49)+\frac{(0.409)(0.591)}{(1)}}}{\Delta} \right]^2$$

n case = 382, n control = 382

* p_2 = P(exposure/control) is prevalence of people who are overweight and obese in normal people without the disease, according to a paper study in Thailand.: Prevalence of overweight and obesity in Thai population: Results of the National Thai Food Consumption Survey. Eating and Weight Disorders (Jitnarin et al., 2011).

** p_1 = P(exposure/case) is prevalence of people who are overweight and obese in people with chronic urticaria which can be calculated from the formula as follows:

$$p_1 = \frac{(0.409)(1.5)}{1+\left[(0.409)((1.5)-1)\right]} = 0.51$$

When, p_2* (exposure/control) = 0.409 and OR = 1.5

3.3 Data Setting

3.3.1 Process

3.3.1.1 Data were collected from the sample population of the intended population of patients diagnosed with chronic urticaria (L50.8) from January 1, 2018 to December 31, 2020, from the statistical unit, Institute of Dermatology.

3.3.1.2 Searching the data of the sample retrospectively individually in the electronic medical record (EMR) of the patient at the outpatient department, Institute of Dermatology.

3.3.1.3 Case and Control Group

1) Case Group

The data were collected and recorded in a case record form, including age, sex, weight, height, body mass index, underlying disease, current medications, symptoms, and laboratory results, including histopathological records (if any) of all patients on their first visit. The groups were divided by body mass index (BMI) (kg/m^2) of the sample as follows: Group 1: BMI < 18.5 = Underweight and BMI 18.5 - 22.9 = Normal Group 2: BMI 23 – 24.9 = Overweight   and BMI $\geq$ 25 = Obesity.

Out of 990 cases diagnosed with chronic urticaria in 2018-2020, 382 cases were selected using a computerized simple random method.

2) Control Group

Select the control group according to the criteria for selecting the control group. Record the control group's data such as age, weight, height, and diagnosed disease at the time of the visit.

From 90,621 new patients in 2018-2020, the control group was randomly selected by a computerized simple random method (n = 382).

3.4 Data Collection

3.4.1 Collect data from electronic medical records (EMR) of patients who come to use the service at the outpatient department, Institute of Dermatology in 2018-2020 (from 1 January 2018 to 31 December 2020) diagnosed with chronic urticaria (L50.8)

3.4.2. Subjects were selected according to inclusion criteria and randomized by computer simple random method (n=382)

3.4.3 Retrospectively searched individually and record the data in the case record form such as age, sex, weight, height, body mass index, underlying disease, current drugs, characteristics, symptoms, duration of disease and laboratory results, including clinical results histopathology.

3.5 Data Analysis

Descriptive statistics was used to depict the characteristics of general information of the sample and control groups, such as frequency, percentage, mean, standard deviation or median, and quartile range. The relationship between overweight/obesity and CSU presented with an Odds ratio (OR) and 95% confidence interval (95% CI). Data were analyzed using IBM SPSS Statistics, Version 23.0 and set to statistically significant at 0.05.

Chapter 4

Research Results

The association between overweight/obesity and chronic spontaneous urticaria. The objective of this study was to study the relationship between overweight/obesity and chronic spontaneous urticaria in Thai patients. The researcher presented the study results as follows:

4.1 Demographic Data

As shown in Table 4.1, the general data of the cases (CSU) were female (75.7%), mean age 39.51 ± 13.51, mean weight 61.19 ± 12.06, mean height 160.96 ± 10.61, and BMI ≥ 23 (49.2%), while the majority of controls (non-CSU) were female (64.9%), mean age 43.24 ± 16.56, mean weight 62.00 ± 13.20, mean height 162.71 ± 8.638 and BMI ≥ 23 (48.4%). Gender, age, and height were statistically significant differences between CSU and non-CSU.

Table 4.1 Demographic Data

Variables	Case (CSU) n=382	Control (Non-CSU) n=382	p-value
Gender			
Male	93 (24.3%)	134 (35.1%)	0.001*
Female	289 (75.7%)	248 (64.9%)	
Age (year)	39.51 ± 13.51	43.24 ± 16.56	0.011*
Weight (kg)	61.19 ± 12.06	62.00 ± 13.20	0.374
Hight (cm)	160.96 ± 10.61	162.71 ± 8.63	0.012*
BMI (kg/m^2)	23.35 ± 4.21	23.44 ± 4.13	0.782
< 18.5	32 (8.4%)	47 (12.3%)	0.842
18.5 - 22.9	162 (42.4%)	150 (39.3%)	

Table 4.1 Demographic Data (Cont.)

Variables	Case (CSU) n=382	Control (Non-CSU) n=382	p-value
BMI (kg/m²)			
23 – 24.9	62 (16.2%)	70 (18.3%)	0.842
≥ 25	126 (33.0%)	115 (30.1%)	
BMI (kg/m²)			
BMI < 23	194 (50.8%)	197 (51.6%)	0.865
BMI ≥ 23	188 (49.2%)	185 (48.4%)	

n = number of samples

4.2 Top 10 Dermatological Diagnoses of the Control Group

As shown in Table 4.2, the top 10 dermatological diagnoses with their corresponding ICD-10 codes within a control group of 382 individuals non-CSU patients. "Dermatitis unspecified" is the most common condition, affecting 18.32% of the control group.

Table 4.2 Top 10 Dermatological Diagnoses of the Control Group

Diagnosis (Total Diagnosis = 107)	ICD-10	Total (%) n=382
Dermatitis Unspecified	L30.9	70 (18.32)
Eczema Xerotic or Asteatosis	L30.82	21 (5.49)
Seborrheic Dermatitis	L21.9	21 (5.49)
Eczema Hand or Feet	L30.81	13 (3.40)
Melasma	L81.1	13 (3.40)
Seborrheic Keratosis	L82.2	12 (3.14)
Face, Melanocytic Nevus	D22.3	8 (2.09)
Tinea Corporis	B35.4.2	8 (2.09)
Irritant Contact Dermatitis	L24	7 (1.83)
Lichen Simplex Chronicus	L28.0.4	7 (1.83)

n = number of samples

4.3 Comparison of the Clinical Characteristics of CSU Patients

As shown in Table 4.3, a comparison of the clinical characteristics of CSU patients between BMI < 23 and BMI ≥ 23. It was found that age (18 – 40 and 41- 64 years) and gender exhibited statistically significant differences between two BMI groups (BMI < 23 and BMI ≥ 23). However, there were no statistically significant differences in other data, including symptoms, underlying diseases, and duration of symptoms.

Table 4.3 Comparison of the Clinical Characteristics of CSU Patients between BMI < 23 and BMI ≥ 23

Variables	BMI < 23 (kg/m^2) n=194	BMI ≥ 23 (kg/m^2) n=188	p-value
Age (year)			
18-40	138 (72.2 %)	73 (42.0%)	<0.001*
41-64	50 (22.7%)	107 (53.7%)	<0.001*
≥ 65	6 (3.1%)	8 (4.3%)	0.546
Gender			
Female	157 (80.9%)	132 (70.2%)	0.015*
Male	37 (19.1%)	56 (29.8%)	
Symptoms			
Wheal	185 (95.4%)	179 (95.2%)	0.946
Wheal & Angioedema	9 (4.6%)	9 (4.8%)	
Underlying Diseases			
Hypertension	4 (2.1%)	10 (5.3%)	0.090
Diabetes	2 (1.0%)	7 (3.7%)	0.083
Dyslipidemia	2 (1.0%)	5 (2.7%)	0.235
Thyroid Disease	2 (1.0%)	7 (3.7%)	0.083
Allergic Rhinitis	7 (3.6%)	7 (3.7%)	0.952
Duration of Symptoms			
≥ 6 months	86 (44.3%)	87 (46.5%)	0.627
< 6 months	108 (55.7%)	100 (53.5%)	

4.4 Comparison of Abnormal Laboratory Investigations of CSU Patients

As shown in Table 4.4, presents the results of abnormal laboratory investigations among CSU patients between BMI < 23 and BMI ≥ 23 with no generally significant differences. However, statistically significant differences were observed in Erythrocyte Sedimentation Rate (ESR) between those two BMI groups.

Table 4.4 Comparison of Abnormal Laboratory Investigations of CSU Patients
between BMI < 23 and BMI ≥ 23

LAB	Total (%)	BMI<23 (kg/m^2)	BMI≥23 (kg/m^2)	p-value
Complete Blood Count	35 (14.5)	21 (8.7%)	14 (5.8%)	0.219
Erythrocyte Sedimentation Rate	16 (17.6)	4 (4.4%)	12 (13.2%)	0.036*
Liver Function Test	2 (3.8)	0 (0.0%)	2 (3.8%)	0.153
Hepatitis Profile	7 (4.4)	3 (1.9%)	4 (2.5%)	0.702
Antinuclear Antibody	59 (28.5)	30 (14.5)	29 (14.0%)	0.888
Urine Analysis	0	0	0	N/A
Stool Exam	0	0	0	N/A
Chest X-Ray	0	0	0	N/A
Thyroid Function	9 (4.6)	3 (1.5%)	6 (3.1%)	0.312
Thyroid Antibody				
Antiperoxidase Antibody	12 (9.2)	5 (3.8%)	7 (5.3%)	0.555
Antithyroglobulin Antibody	19 (14.5)	9 (6.9%)	10 (7.6%)	0.812

4.5 The Association between Overweight/Obesity and CSU

As shown in Table 4.5, the association between overweight/obesity and CSU, with BMI classified into four groups: BMI < 18.5 (OR = 0.61), BMI 18.5 - 22.9 (reference), BMI 23 - 24.9 (OR = 0.82), and BMI > 25 (OR= 1.01). The findings indicate that there were no statistically significant associations between classified BMI and CSU. Also, there were no statistically significant associations between BMI ≥ 23 (OR = 1.03) and CSU. In summary, the findings suggest that there is no statistically significant association between overweight/obesity and CSU.

Table 4.5 The Association between Overweight/Obesity and CSU

	Odd Ratio (OR)	95% CI	p -value
BMI (kg/m^2)			
< 18.5	0.61	0.37 – 1.01	0.053
18.5 - 22.9	Reference	N/A	N/A
23 - 24.9	0.82	0.54 – 1.23	0.325
> 25	1.01	0.72 – 1.41	0.962
BMI (kg/m^2)			
BMI < 23	Reference	N/A	N/A
BMI ≥ 23	1.03	0.78 – 1.37	0.828

4.6 Discussion

Our study is a case-control study conducted on patients with CSU. The main objective of our study was to find the possible relationship between overweight/obesity and CSU among adults within our specific population. Upon analyzing the data, the results indicated that there was no significant association between being overweight or obese and the presence of CSU (odds ratio = 1.03, 95% confidence interval 0.78-1.37, p-value = 0.828). These findings were not consistent with numerous previous studies that were reviewed in the literature (Lapi et al., 2016; Zbiciak-Nylec et al., 2018; Shalom et al., 2018; Kim et.al., 2019; Choudhary & Shrestha, 2020). Nevertheless, there were a few studies in the past that did support our

findings. For instance, Soria et al. (2018) conducted a study utilizing a French cohort of 278 patients with CU (CSU & CIU) which is a national, non-interventional, multicenter study. Their study specifically examined BMI and waist circumference as indicators of obesity. The results from their study indicated that obesity was not associated with severe chronic urticaria, which was like the outcomes of our study.

Basic demographic data of the normal population in Westerns were different from Orientals, that was one of the various results of our study. Our study used a case-control study as a method which was different from other studies that used Cross-sectional (Lapi et al., 2016; Shalom et al., 2018), Cohort (Kim et al., 2019), and observational studies (Zbiciak-Nylec et al., 2018; Choudhary & Shrestha, 2020). However, the main difference distinguishing our study from other studies, except for some studies in Asia (Kim et al., 2019; Choudhary & Shrestha, 2020), was the criteria for dividing BMI. The adoption of different BMI standards for different populations is crucial for accurate health risk assessment. Asian populations with a BMI that might be considered normal under WHO standards could actually be at a higher risk of health issues typically associated with overweight or obesity. For adults, there are two commonly accepted BMI classifications: 1) the standard set by the World Health Organization (WHO) and 2) the standard set by the World Health Organization, Regional Office for the Western Pacific (WPRO). These classifications were utilized for the purpose of categorizing individuals as overweight or obese. In accordance with the WHO guidelines, BMI falls into three categories: normal (18.5 - 24.9), overweight (25 - 29.9), and obese ($\geq$ 30). While the WHO criteria have gained widespread acceptance and are extensively utilized on a global scale, there is evidence suggesting that the WHO standard may not be suitable for categorizing obesity in Asian populations. This is due to variations in body fat percentages and body composition among different ethnic groups. Asians typically show a greater proportion of body fat compared to individuals of Caucasians who are of similar age, gender, and BMI. The greater proportion of body fat at a lower BMI is indicative of a heightened susceptibility to various diseases such as heart disease and diabetes, as well as risk factors associated with chronic illnesses and mortality at a lower BMI. Additionally, the prevalence of risk factors for type 2 diabetes and cardiovascular disease among

Asian individuals remains significant even when their BMI is below the current WHO threshold of 25 kg/m^2 (WHO Expert Consultation, 2004). To address this discrepancy, our study employed the World Health Organization, Regional Office for the Western Pacific (WPRO) standards, as recommended by the International Association for the Study of Obesity and the International Obesity Task Force (IOTF) since 2000. These standards propose more applicable and appropriate BMI cut-off points for Asian populations, BMI is classified as: normal (18.5 - 22.9), overweight (23 - 24.9), and obese (≥25) (Deurenberg, Deurenberg-Yap, & Guricci, 2002; Low, Chin, Ma, Heng, & Deurenberg-Yap, 2009; Jitnarin et al., 2011). This classification reflects a tailored approach to assessing and managing health risks associated with body weight in Asian populations, ensuring a more accurate and relevant health risk assessment framework.

In our study, there were more women than men in CSU patients, and the peak incidence of CSU was 20 – 40 years (58.37%), which is in accordance with several studies (Lapi et al., 2016; Chu, Cho, Jiang, Lin, & Tang, 2017; Moestrup et al., 2017; Kim, Yang, Choi, Choi, & Youn, 2018; Ghazanfar, Kibsgaard, Thomsen, & Vestergaard, 2020). This gender disparity in CU incidence is a well-recognized phenomenon in dermatological research. Many studies have observed that CU, including CSU, exhibits a significant female preponderance, with an average female-to-male ratio ranging approximately from 2: 1 to 4: 1 (Cassano, Colombo, Bellia, Zagni, & Vena, 2016). Furthermore, hormonal fluctuations—such as those experienced during the menstrual cycle, pregnancy, menopause, and with the use of hormonal contraceptives or hormone replacement therapy—have been implicated in the pathogenesis of urticarial lesions (Kalkan, Bas, & Pancar, 2013). However, our study did not delve into these hormonal aspects, suggesting an area for future research. The observed gender disparity extends beyond mere incidence rates to encompass broader gender-related differences in CSU, including pathophysiology, clinical presentation, and the association with comorbid conditions, such as overweight/obesity. Ghazanfar et al. (2020) highlighted that gender-dependent variations in CSU might reflect not only biological differences but also disparities in healthcare-seeking behavior, with men less likely to seek medical attention than women. This tendency, influenced by personal beliefs, social norms, and economic

status (Galdas, Cheater, & Marshall, 2005; Abdullah, Arsat, Aziz, & Al-Kubaisy, 2022), and which similar to our study in that the majority of the study population were women, which might also reflect a greater propensity among women to seek care for CSU symptoms.

In our study, ESR was the only abnormal laboratory investigation among CSU patients that showed statistically significant differences between BMI < 23 and BMI ≥ 23 (p-value = 0.036). This finding aligns with the updated International EAACI/GA^{2}LEN/ EuroGuiDerm/APAAACI guidelines, which recommend a differential blood count and C-reactive protein (CRP) and/or ESR for CSU all patients and total IgE and IG-anti-TPO for those requiring special care (Zuberbier et al., 2022). The ESR and CRP are widely utilized laboratory tests for assessing inflammation and are essential for the monitoring and diagnosis of inflammatory conditions. Many studies reported ESR has been found to be higher in patients with CSU compared to healthy controls (Ferriani et al., 2015; Akca & Tuncer Kara, 2020; Kaya & Mermutlu, 2022). Some studies offer clinicians valuable insights by corroborating clinical manifestations of inflammation, despite ESR not being specific to any particular disease and being influenced by various disease factors (Bray et al., 2016; Lapić, Padoan, Bozzato, & Plebani, 2020). Meanwhile, obesity is associated with chronic inflammation, which plays a role in the development of various pathological conditions (Karczewcki et al., 2018). It is known to be associated with elevated levels of inflammatory markers. Research by Cohen, Margalit, Shochat, Goldberg, & Krause (2021) highlighted a direct correlation between BMI and markers of inflammation such as white blood cell count, platelet count, ESR, and CRP, particularly pronounced in individuals with morbid obesity. Sharma, Kumar, Jha, Agarwal, & Misra (2020) reported that approximately one-fifth of patients with rheumatoid arthritis, who were actually in low disease activity, had elevated inflammatory markers, primarily due to obesity. This study emphasizes the importance of considering obesity when interpreting inflammatory markers, as obesity itself may cause modest elevations of ESR or CRP. However, the relationship between inflammatory markers like ESR and CRP, and their interaction with BMI (overweight/obesity) in CSU and other inflammatory conditions, is complex and influenced by various factors, but this

finding from our study also supported previous studies suggesting that CSU and overweight/obesity may be linked through pathogenetic involvement in the inflammatory process (Zbiciak-Nylec et al., 2018; Matano et al., 2020).

The relationship between the inflammatory processes underlying obesity and CSU remains elusive, despite mounting evidence pointing towards a shared inflammatory pathway. Notably, Grzanka, Damasiewicz-Bodzek, & Kasperska-Zajac (2019) highlighted a correlation between CSU and activation of the TNF-α/receptors signaling pathway, marked by elevated levels of TNF-α, sTNF-R1, and sTNF-R2. These findings suggest a significant interplay in the inflammatory response associated with CSU. Similarly, Vena & Cassano (2017) identified potential overlaps between CSU and MS, encompassing shared concerns such as inflammation, oxidative stress, alterations in adipokine levels, and activation of the coagulation system. This underscores the multifaceted nature of the inflammatory response in CSU, which may extend beyond traditional pathways. Recent studies have further expanded our understanding of this association. Luo et al. (2023) uncovered alterations in the gut microbiota of CSU patients, including increased α-diversity and shifts in the abundance of key bacterial phyla such as Firmicutes, Bacteroidetes, and Proteobacteria. These changes in the gut microbiota and its metabolites are thought to influence the immune and inflammatory responses, potentially contributing to the pathogenesis of CSU. Furthermore, Farres, Mahmoud, Eissa, & Elkady (2022) provided evidence of enhanced production of CRP, leptin, and pro-inflammatory cytokines in obese CSU patients, alongside increased spontaneous production of interleukin-4 (IL-4) and TNF-α. This suggests that obesity exacerbates the chronic inflammation and immune system imbalance observed in CSU, with both conditions fostering a sustained low-grade systemic inflammation characterized predominantly by TNF-α and other inflammatory mediators. These studies collectively underscore the critical role of inflammation in the pathogenesis of CSU among obese individuals. They suggest that the link between obesity and CSU may be rooted in chronic inflammation and immune system dysregulation, highlighting the importance of considering inflammatory markers and pathways in understanding and managing CSU in the context of obesity.

Although, there have many studies explored the relationship between overweight/obesity and CSU, but the etiopathogenesis of CSU has not been completely understood. Despite, our study found no statistically significant association between overweight/obesity and CSU in Thai population, we suggest that larger populations, prospective study, or multicenter population are necessary in the future to improve our understanding of this relationship and clarify our results. These studies would help to shed light on the possible association between overweight/obesity and CSU and could lead to the development of targeted interventions for patients with CSU.

The limitations of this study are multifaceted, reflecting both the constraints of our methodological approach and the challenges inherent in clinical diagnosis. Firstly, the use of a retrospective case-control design, while beneficial for examining existing data, introduces inherent risks related to data accuracy and completeness. Despite employing a rigorous set of inclusion and exclusion criteria to select our case and control groups, the potential for selection and recall biases remains a significant concern. These biases are common in case-control studies and can impact the validity of our findings. Secondly, the absence of a specific International Classification of Diseases, Tenth Revision (ICD-10) code for CSU complicates the identification and classification of cases. This limitation, shared by other studies in the field (e.g., Lapi et al., 2016), raises the possibility of misclassification. Although we sought to mitigate this issue through stringent inclusion and exclusion criteria and by relying on diagnoses made by specialized dermatologists at a tertiary dermatology institute, the risk of diagnostic inaccuracies cannot be entirely eliminated. Lastly, our approach to measuring body weight, height, and body mass index (BMI) was designed to align with standardized practices in real-world clinical settings, which lends credibility to our measurements. However, the potential for misdiagnosis and the influence of unidentified confounding factors present challenges to the internal validity of our study. The effects of such factors were not fully adjustable, which may have implications for the interpretation and generalizability of our findings (Kim et al., 2019).

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

Our study has revealed that the elevated ESR observed in individuals within the overweight/obesity group may support a pathogenetic link to CSU. This suggests that overweight and obesity could be implicated in the inflammatory processes associated with CSU. However, our study did not find an association between overweight/ obesity and CSU in the adult Thai population, diverging from the conclusions of many previous studies. Nevertheless, our findings are consistent with a few previous studies, signifying an intricate and possibly subtle correlation between an individual's body mass and CSU. Considering the conflicting evidence in this domain, it is evident that conducting further research is imperative. Future studies are essential to validate our findings and further explore the possible connections between overweight/ obesity and CSU, potentially uncovering new insights into their pathophysiological interactions. This continued investigation is crucial for developing targeted interventions and improving outcomes for individuals affected by CSU.

5.2 Recommendations

To enhance the understanding of the relationship between overweight/obesity and chronic spontaneous urticaria, and to validate the findings of this study, we recommend the following approaches for future study.

5.2.1 We suggest considering a larger, more diverse population, prospective studies, or utilizing multicenter populations, contributing to a more comprehensive analysis, and improving our understanding of this relationship, and clarifying our results.

5.2.2 Including additional parameters to indicate overweight and obesity such as waist circumference, waist-to-hip ratio, and body fat percentage, may potentially provide a more comprehensive comprehension of overweight and obesity.

5.2.3 Enhanced laboratory investigations are recommended to further elucidate the underlying mechanisms linking overweight/ obesity to CSU. This includes but is not limited to, the assessment of inflammatory markers (e.g., CRP, interleukin). These investigations could provide insight into the metabolic and inflammatory pathways involved in this association.

5.2.4 Given the complex interplay between MS and CSU, future studies should aim to thoroughly evaluate the metabolic health of participants. This encompasses a detailed assessment of glucose tolerance, lipid profiles, and blood pressure, among others, to better understand the metabolic context in which CSU occurs in individuals with overweight/obesity.

5.2.5 Other Factors Associated with CSU. These include hormonal imbalances, alterations in gut microbiota, and vitamin deficiencies. Recent studies have begun to shed light on less explored, yet potentially significant, factors that may contribute to the development and exacerbation of CSU.

References

Abdullah, N. N., Arsat, M. H. M., Aziz, N. R. A., & Al-Kubaisy, W. (2022). Men health seeking behavior: A literature review. *Environment-behaviour proceedings journal, 7*(20), 247-254. doi:10.21834/ebpj.v7i20.3484

Aekplakorn, W., Inthawong, R., Kessomboon, P., Sangthong, R., Chariyalertsak, S., Putwatana, P., & Taneepanichskul, S. (2014). Prevalence and trends of obesity and association with socioeconomic status in Thai adults: National health examination surveys, 1991-2009. *Journal of obesity, 2014*, 410259. doi:10.1155/2014/410259

Agyemang, C., Meeks, K., Beune, E., Owusu-Dabo, E., Mockenhaupt, F. P., Addo, J., … Stronks, K. (2016). Obesity and type 2 diabetes in sub-Saharan Africans - Is the burden in today's Africa similar to African migrants in Europe? The RODAM study. *BMC medicine*, *14*(1), 166. doi:10.1186/s12916-016-0709-0

Akca, H. M., & Tuncer Kara, K. (2020). Correlation of urticaria activity score in chronic spontaneous urticaria with serum C-reactive protein level and neutrophil/lymphocyte ratio. *Dermatologic therapy*, *33*(6), e14532. doi: 10.1111/dth.14532

American Diabetes Association (2018). 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2018*. *Diabetes care*, *41*(Suppl 1), S13–S27. doi:10.2337/dc18-S002

Anandacoomarasamy, A., Fransen, M., & March, L. (2009). Obesity and the musculoskeletal system. *Current opinion in rheumatology*, *21*(1), 71–77. doi: 10.1097/bor.0b013e32831bc0d7

Antia, C., Baquerizo, K., Korman, A., Alikhan, A., & Bernstein, J. A. (2018). Urticaria: A comprehensive review: Treatment of chronic urticaria, special populations, and disease outcomes. *Journal of the American Academy of Dermatology*, *79*(4), 617–633. doi:10.1016/j.jaad.2018.01.023

Armstrong, A. W., Soong, W., & Bernstein, J. A. (2023). Chronic Spontaneous Urticaria: How to Measure It and the Need to Define Treatment Success. *Dermatology and therapy*, *13*(8), 1629–1646. doi:10.1007/s13555-023-00955-7

References (Cont.)

Bäck, O., & Larsen, A. (1978). Delayed cold urticaria. *Acta dermato-venereologica, 58*(4), 369–371.

Banadyha, N. V. & Nakonechna, A. A. (2022). Clinical aspects of acute urticaria in children in the practice of primary and secondary medical care. *Modern pediatrics. Ukraine*, 11-17. doi:10.15574/SP.2022.121.11

Bansal, C. J., & Bansal, A. S. (2019). Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. *Allergy, asthma, and clinical immunology: official journal of the Canadian Society of Allergy and Clinical Immunology*, *15*, 56. doi:10.1186/s13223-019-0372-z

Baudy, A., Bessis, D., & Raison-Peyron, N. (2022). Rare concomitant association between an acquired aquagenic keratoderma and an aquagenic urticaria. *Clinical and experimental dermatology*, *47*(7), 1376–1377. doi:10.1111/ced.15188

Bhatia, R., Alikhan, A., & Maibach, H. I. (2009). Contact urticaria: present scenario. *Indian journal of dermatology*, *54*(3), 264–268. doi:10.4103/0019-5154.55639

Bianchi, L., Hansel, K., Biondi, F., Napolitano, M., Patruno, C., Fabbrocini, G., … Stingeni, L. (2022). Delayed urticaria after the third dose of mRNA COVID19 vaccine: A case series. *Dermatologic therapy, 35*(9), e15680. doi:10.1111/dth.15680

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*, *2*(2), 1143–1211. doi:10.1002/cphy.c110025

Bray, C., Bell, L. N., Liang, H., Haykal, R., Kaiksow, F., Mazza, J. J., & Yale, S. H. (2016). Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ: Official Publication of the State Medical Society of Wisconsin*, *115*(6), 317-321.

Carra, S., Dereure, O., & Raison-Peyron, N. (2022). A localized salt-dependent aquagenic urticaria successfully treated with omalizumab. *Clinical and experimental dermatology*, *47*(12), 2339–2341. doi:10.1111/ced.15346

References (Cont.)

Cassano, N., Colombo, D., Bellia, G., Zagni, E., & Vena, G. A. (2016). Gender-related differences in chronic urticaria. *Giornale italiano di dermatologia e venereologia: organo ufficiale, Societa italiana di dermatologia e sifilografia*, *151*(5), 544–552.

Choudhary, D. & Shrestha, S, Y. (2020). Association of obesity with chronic idiopathic urticaria at birat medical college and teaching hospital. *Birat Journal of Health Sciences, 5*, 1087-1090. doi:10.3126/bjhs.v5i2.31411

Chu, C. Y., Cho, Y. T., Jiang, J. H., Lin, E. I., & Tang, C. H. (2017). Epidemiology and comorbidities of patients with chronic urticaria in Taiwan: A nationwide population-based study. *Journal of dermatological science*, *88*(2), 192–198. doi:10.1016/j.jdermsci.2017.07.006

Chung, S. D., Wang, K. H., Tsai, M. C., Lin, H. C., & Chen, C. H. (2016). Hyperlipidemia is associated with chronic urticaria: A population-based study. *PLOS One*, *11*(3), e0150304. doi:10.1371/journal.pone.0150304

Coelho, I., Neto, B., Bordalo, D., & Jacob, S. (2022). Urticaria in a Pediatric Population: A Portuguese Single-Center Cohort Report. *Cureus, 14*(7), e26659. doi:10.7759/cureus.26659

Cohen, E., Margalit, I., Shochat, T., Goldberg, E., & Krause, I. (2021). Markers of chronic inflammation in overweight and obese individuals and the role of gender: A cross-sectional study of a large cohort. *Journal of inflammation research*, *14*, 567–573. doi:10.2147/JIR.S294368

Colchero, M. A., Popkin, B. M., Rivera, J. A., & Ng, S. W. (2016). Beverage purchases from stores in Mexico under the excise tax on sugar sweetened beverages: observational study. *BMJ (Clinical research ed.)*, *352*, h6704. doi:10.1136/bmj.h6704

Copaescu, A., Gibson, A., Li, Y., Trubiano, J. A., & Phillips, E. J. (2021). An Updated Review of the Diagnostic Methods in Delayed Drug Hypersensitivity. *Frontiers in pharmacology, 11*, 573573. doi:10.3389/fphar.2020.573573

References (Cont.)

Cunha, C., Gonçalves, S. M., Duarte-Oliveira, C., Leite, L., Lagrou, K., Marques, A., … Carvalho, A. (2017). IL-10 overexpression predisposes to invasive aspergillosis by suppressing antifungal immunity. *The Journal of allergy and clinical immunology, 140(*3), 867–870.e9. doi:10.1016/j.jaci.2017.02.034

Deurenberg, P., Deurenberg-Yap, M., & Guricci, S. (2002). Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, *3*(3), 141–146. doi:10.1046/j.1467-789x. 2002.00065.x

Drivenes, J. L., Banerji, A., & Bygum, A. (2022). Delayed onset urticaria and symptomatic dermographism following COVID-19 booster vaccination: A case series. *Clinical and translational allergy, 12*(11), e12206. doi:10.1002/clt2.12206

Engin, A. (2017). The Definition and Prevalence of Obesity and Metabolic Syndrome. *Advances in experimental medicine and biology*, *960*, 1–17. doi:10.1007/978-3-319-48382-5_1

Ensina, L. F., Min, T. K., Félix, M. M. R., de Alcântara, C. T., & Costa, C. (2022). Acute Urticaria and Anaphylaxis: Differences and Similarities in Clinical Management. *Frontiers in allergy*, 3, 840999. doi:10.3389/falgy.2022.840999

Ercan, N., Ozmen, S., & Bostanci, I. (2019). A rare case of localized aquagenic urticaria in a preschool child, including a literature review. *Revue Francaise D Allergologie, 59*(6), 411-414. doi: 10.1016/J.REVAL.2019.05.003

Farres, M. N., Mahmoud, M. M., Eissa, N. M., & Elkady, H. M. (2022). Assessment of serum leptin in patients with chronic spontaneous urticaria. *The Egyptian Journal of Hospital Medicine, 89*(1), 6006-6010. doi:10.21608/ejhm.2022 .266832

References (Cont.)

Ferriani, M. P., Silva, M. F., Pereira, R. M., Terreri, M. T., Saad Magalhães, C.,
    Bonfá, E., … Silva, C. A. (2015). Chronic spontaneous urticaria: A survey of
    852 cases of childhood-onset systemic lupus erythematosus. *International
    archives of allergy and immunology*, *167*(3), 186–192. doi:10.1159/
    000438723

Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M.,
    Lindgren, C. M., … McCarthy, M. I. (2007). A common variant in the FTO
    gene is associated with body mass index and predisposes to childhood and
    adult obesity. *Science (New York, N.Y.)*, *316*(5826), 889–894.
    doi:10.1126/science.1141634

Fukayama, M., Domoto, Y., Sato, S., & Asano, Y. (2021). Case of aquagenic urticaria:
    Case report and the results of histopathological examination. *The Journal of
    dermatology*, *48*(1), 88–91. doi:10.1111/1346-8138.15615

Fukunaga, A., Oda, Y., Imamura, S., Mizuno, M., Fukumoto, T., & Washio, K.
    (2023). Cholinergic Urticaria: Subtype Classification and Clinical Approach.
    American journal of clinical dermatology, 24(1), 41–54. doi:10.1007/s40257-
    022-00728-6

Fukunaga, A., Washio, K., Hatakeyama, M., Oda, Y., Ogura, K., Horikawa, T., &
    Nishigori, C. (2018). Cholinergic urticaria: epidemiology, physiopathology,
    new categorization, and management. *Clinical autonomic research : official
    journal of the Clinical Autonomic Research Society*, *28*(1), 103–113.
    doi:10.1007/s10286-017-0418-6

Galdas, P. M., Cheater, F., & Marshall, P. (2005). Men and health help-seeking
    behaviour: literature review. *Journal of advanced nursing*, *49*(6), 616-623.
    doi:10.1111/j.1365-2648.2004.03331.x

Gandhi, C., Healy, C., Wanderer, A. A., & Hoffman, H. M. (2009). Familial atypical
    cold urticaria: description of a new hereditary disease. *The Journal of allergy
    and clinical immunology, 124*(6), 1245–1250. doi:10.1016/j.jaci.2009.09.035

References (Cont.)

Gatica-Ortega, M. E., Sánchez-Matas, I., Sánchez-Muñoz, L., & Pastor-Nieto, M. A. (2022). Acquired vibratory angioedema with a severe impact on work performance. *Occupational medicine (Oxford, England), 72*(8), 566–569. doi:10.1093/occmed/kqac092

Ghazanfar, M. N., Kibsgaard, L., Thomsen, S. F., & Vestergaard, C. (2020). Risk of comorbidities in patients diagnosed with chronic urticaria: A nationwide registry-study. *The World Allergy Organization journal*, *13*(1), 100097. doi:10.1016/j.waojou.2019.100097

Giménez-Arnau, A. M., Ribas-Llauradó, C., Mohammad-Porras, N., Deza, G., Pujol, R. M., & Gimeno, R. (2022). IgE and high-affinity IgE receptor in chronic inducible urticaria, pathogenic, and management relevance. *Clinical and translational allergy*, *12*(2), e12117. doi:10.1002/clt2.12117

Goda, A., & Masuyama, T. (2016). Obesity and overweight in asian people. *Circulation Journal: Official Journal of the Japanese Circulation Society*, *80*(12), 2425–2426. doi:10.1253/circj.CJ-16-1087

Greaves, M. W., & O'Donnell, B. F. (1998). Not all chronic urticaria is "idiopathic"!. *Experimental dermatology, 7*(1), 11–13. doi:10.1111/j.1600-0625.1998.tb00296.x

Grieco, T., Ambrosio, L., Trovato, F., Vitiello, M., Demofonte, I., Fanto, M., … Pellacani, G. (2022). Effects of Vaccination against COVID-19 in Chronic Spontaneous and Inducible Urticaria (CSU/CIU) Patients: A Monocentric Study. *Journal of clinical medicine*, *11*(7), 1822. doi:10.3390/jcm11071822

Grundy S. M. (2004). Obesity, metabolic syndrome, and cardiovascular disease. *The Journal of clinical endocrinology and metabolism*, *89*(6), 2595–2600. doi:10.1210/jc.2004-0372

Grzanka, R., Damasiewicz-Bodzek, A., & Kasperska-Zajac, A. (2019). Tumor necrosis factor-alpha and Fas/Fas ligand signaling pathways in chronic spontaneous urticaria. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology*, *15*, 15. doi:10.1186/s13223-019-0332-7

References (Cont.)

Guarneri, F., Guarneri, C., & Marini, H. R. (2014). Amitriptyline and bromazepam in the treatment of vibratory angioedema: which role for neuroinflammation?. *Dermatologic therapy*, *27*(6), 361–364. doi:10.1111/dth.12150

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2020). Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. *NCHS data brief*, (360), 1–8.

Hoffman, H. M., Wright, F. A., Broide, D. H., Wanderer, A. A., & Kolodner, R. D. (2000). Identification of a locus on chromosome 1q44 for familial cold urticaria. *American journal of human genetics, 66*(5), 1693–1698. doi:10.1086/302874

Hong, D., Weng, J., Ye, M., & Liu, Y. (2023). Efficacy of different oral H_1 antihistamine treatments on allergic rhinitis: a systematic review and network meta-analysis of randomized controlled trials. *Brazilian journal of otorhinolaryngology, 89*(4), 101272. doi:10.1016/j.bjorl.2023.03.009.

Hsieh, J., & Lee, J. K. (2017). Chronic spontaneous urticaria. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 189*(2), E77. doi:10.1503/cmaj.150951

Hu, L. Y., Liu, C. J., Lu, T., Hu, T. M., Tsai, C. F., Hu, Y. W., … Su, T. P. (2013). Delayed onset urticaria in depressive patients with bupropion prescription: a nationwide population-based study. *PloS one, 8*(11), e80064. doi:10.1371/journal.pone.0080064

Jaabouti, G., Benchidmi, S., Hafidi, N. E., Bencchakroun, S., & Mahraoui, C. (2023). A Case Report On Aquagenic Urticaria . *Asian Journal of Medicine and Health*, *21*(9), 101–105. doi:10.9734/ajmah/2023/v21i9863

Jitnarin, N., Kosulwat, V., Rojroongwasinkul, N., Boonpraderm, A., Haddock, C. K., & Poston, W. S. (2011). Prevalence of overweight and obesity in Thai population: results of the National Thai Food Consumption Survey. *Eating and weight disorders: EWD*, *16*(4), e242-e249. doi:10.1007/BF03327467

References (Cont.)

Kalathoor, I. (2015). Snoring-Induced Vibratory Angioedema. *The American journal of case reports*, *16*, 700–702. doi:10.12659/AJCR.894636

Karczewski, J., Śledzińska, E., Baturo, A., Jończyk, I., Maleszko, A., Samborski, P., … Dobrowolska, A. (2018). Obesity and inflammation. *European cytokine network*, *29*(3), 83–94. doi:10.1684/ ecn.2018.0415

Kalkan, G., Pancar, G. S., Baş, Y. (2013). A case of chronic urticaria exacerbating with menstrual cycles. *Journal of contemporary medicine, 3*(3), 200-202.

Kaya, O., & Mermutlu, S. I. (2022). Monocyte-to-HDL cholesterol ratio as a new parameter of systemic inflammation and disease severity in treatment-resistant chronic spontaneous urticaria. *Journal of basic and clinical health sciences, 71*(1), 501-506. doi:10.30621/jbachs.1210134

Khan, D. A. (2013). Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *The journal of allergy and clinical immunology. In practice*, *1*(5), 433–440.e1. doi:10.1016/j.jaip.2013.06.003

Kim, B. R., Yang, S., Choi, J. W., Choi, C. W., & Youn, S. W. (2018). Epidemiology and comorbidities of patients with chronic urticaria in Korea: A nationwide population-based study. *The Journal of dermatology, 45*(1), 10-16. doi:10.1111/1346-8138.14075

Kim, Y. S., Han, K., Lee, J. H., Lee, J. Y., & Park, Y. M. (2019). Can Body Mass Index and/or Waist Circumference Be the Risk Factors of Chronic Spontaneous Urticaria?: A Nationwide Population-Based Study. *Annals of dermatology*, *31*(4), 482–485. doi:10.5021/ad.2019.31.4.482

Kolkhir, P., Altrichter, S., Munoz, M., Hawro, T., & Maurer, M. (2020). New treatments for chronic urticaria. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*, *124*(1), 2–12. doi:10.1016/j.anai.2019.08.014

Kolkhir, P., Giménez-Arnau, A. M., Kulthanan, K., Peter, J., Metz, M., & Maurer, M. (2022). Urticaria. *Nature reviews. Disease primers, 8*(1), 61. doi:10.1038/s41572-022-00389-z

References (Cont.)

Konttinen, H., Haukkala, A., Sarlio-Lähteenkorva, S., Silventoinen, K., & Jousilahti, P. (2009). Eating styles, self-control and obesity indicators. The moderating role of obesity status and dieting history on restrained eating. *Appetite*, *53*(1), 131–134. doi:10.1016/j.appet.2009.05.001

Kränke, B., & Mayr-Kanhäuser, S. (2002). Cold urticaria and angiotensin converting enzyme inhibitor. *Acta dermato-venereologica, 82*(2), 149–150. doi:10.1080/00015550252948284

Kulthanan, K., Church, M. K., Grekowitz, E. M., Hawro, T., Kiefer, L. A., Munprom, K., … Maurer, M. (2022). Evidence for histamine release in chronic inducible urticaria - A systematic review. *Frontiers in immunology*, *13*, 901851. doi:10.3389/fimmu.2022.901851

Kulthanan, K., Tuchinda, P., Chularojanamontri, L., Chanyachailert, P., Korkij, W., Chunharas, A., … Ngamphaiboon, J. (2016). Clinical practice guideline for diagnosis and management of urticaria. *Asian Pacific journal of allergy and immunology*, *34*(3), 190–200.

Kumaran, M. S., Arora, A. K., & Parsad, D. (2017). Cholinergic urticaria: Clinicoepidemiological paradigms from a tertiary care center in North India. *Indian journal of dermatology, venereology and leprology*, *83*(5), 599–601. doi:10.4103/ijdvl.IJDVL_735_16

LaCava, A. F., & Fadugba, O. O. (2023). Cyclosporine for omalizumab-refractory chronic urticaria: a report of five cases. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology*, *19*(1), 78. doi:10.1186/s13223-023-00820-4

Lapi, F., Cassano, N., Pegoraro, V., Cataldo, N., Heiman, F., Cricelli, I., … Vena, G. A. (2016). Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. *The British Journal of Dermatology, 174*(5), 996-1004. doi:10.1111/bjd.14470

Lapić, I., Padoan, A., Bozzato, D., & Plebani, M. (2020). Erythrocyte sedimentation rate and c-reactive protein in acute inflammation. *American journal of clinical pathology*, *153*(1), 14-29. doi:10.1093/ajcp/aqz142

References (Cont.)

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., Straif, K., & International Agency for Research on Cancer Handbook Working Group (2016). Body Fatness and Cancer--Viewpoint of the IARC Working Group. *The New England journal of medicine*, *375*(8), 794–798. doi:10.1056/NEJMsr1606602.

Legat, F. J. (2023). Aquagenic pruritus indicates increased risks in patients with myeloproliferative neoplasms. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *37*(6), 1095–1096. doi:10.1111/jdv.19107

Levine, J. A., Eberhardt, N. L., & Jensen, M. D. (1999). Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science (New York, N.Y.)*, *283*(5399), 212–214. doi:10.1126/science.283.5399.212

Littleton, S. W. (2012). Impact of obesity on respiratory function. *Respirology (Carlton, Vic.)*, *17*(1), 43–49. doi:10.1111/j.1440-1843.2011.02096.x

Loos, R. J. (2018). The genetics of adiposity. *Current opinion in genetics & development*, *50*, 86–95. doi:10.1016/j.gde.2018.02.009

Low, S., Chin, M. C., Ma, S., Heng, D., & Deurenberg-Yap, M. (2009). Rationale for redefining obesity in Asians. *Annals of the Academy of Medicine, Singapore, 38*(1), 66-69.

Luo, Z., Jin, Z., Tao, X., Wang, T., Wei, P., Zhu, C., & Wang, Z. (2023). Combined microbiome and metabolome analysis of gut microbiota and metabolite interactions in chronic spontaneous urticaria. *Frontiers in cellular and infection microbiology*, *12*, 1094737. doi:10.3389/fcimb.2022.1094737

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of general psychiatry*, *67*(3), 220–229. doi:10.1001/archgenpsychiatry.2010.2

Maibach, H. I., & Johnson, H. L. (1975). Contact urticaria syndrome. Contact urticaria to diethyltoluamide (immediate-type hypersensitivity). *Archives of dermatology*, *111*(6), 726–730. doi:10.1001/archderm.111.6.726

References (Cont.)

Malik, V. S., Willett, W. C., & Hu, F. B. (2013). Global obesity: trends, risk factors and policy implications. *Nature reviews. Endocrinology*, *9*(1), 13–27. doi:10.1038/nrendo.2012.199

Martens, P. M., & Berrens, L. (1975). Enzyme activation and inhibition induced by cold provocation in a patient with cold urticaria. *Acta dermato-venereologica, 55*(2), 121–125.

Matano, Y., Morita, T., Ito, M., Okazaki, S., Koto, M., Ichikawa, Y., … Kanda, N. (2020). Dietary habits in Japanese patients with chronic spontaneous urticaria. *The Australasian Journal of Dermatology*, *61*(3), e333-e338. doi:10.1111/ajd.13283

Maurer, M., Metz, M., Brehler, R., Hillen, U., Jakob, T., Mahler, V., … Magerl, M. (2018). Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. *The Journal of allergy and clinical immunology, 14*1(2), 638–649. doi:10.1016/j.jaci.2017.06.032

Maurer, M., Zuberbier, T., & Metz, M. (2022). The Classification, Pathogenesis, Diagnostic Workup, and Management of Urticaria: An Update. *Handbook of experimental pharmacology, 268*, 117–133. doi:10.1007/164_2021_506

Melikoglu, M., Pala, E., & Bayraktar, M. (2022). Etiological causes in patients with acute urticaria and angioedema: A cross-sectional study. *Allergologia et immunopathologia*, *50*(S Pt 2), 15–23. doi:10.15586/aei.v50iSP2.784

Miossec, P., Sullivan, T. J., Tharp, M. D., Volant, A., & Le Goff, P. (1987). Acute synovial fluid eosinophilia associated with delayed pressure urticaria: a role for mast cells?. *The Journal of rheumatology, 14*(2), 372–374.

Mizuno, M., Oda, Y., Imamura, S., Washio, K., Fukumoto, T., & Fukunaga, A. (2022). IgE receptor responsiveness of basophils in chronic inducible urticaria. *Frontiers in immunology, 13*, 995596. doi:10.3389/fimmu.2022.995596

Moestrup, K., Ghazanfar, M. N., & Thomsen, S. F. (2017). Patient-reported outcomes (PROs) in chronic urticaria. *International Journal of Dermatology*, *56*(12), 1342–1348. doi:10.1111/ijd.13668

References (Cont.)

Moñino-Romero, S., Kolkhir, P., Szépfalusi, Z., Schoepke, N., Metz, M., Asero, R., … Altrichter, S. (2023). In chronic spontaneous urticaria soluble FcεRI is elevated and linked to atopy and chronic inducible urticaria. *Clinical and translational allergy*, *13*(7), e12272. doi:10.1002/clt2.12272

Morioke, S., Takahagi, S., Iwamoto, K., Shindo, H., Mihara, S., Kameyoshi, Y., & Hide, M. (2010). Pressure challenge test and histopathological inspections for 17 Japanese cases with clinically diagnosed delayed pressure urticaria. *Archives of dermatological research, 302*(8), 613–617. doi:10.1007/s00403-010-1053-4

Murdaca, G., Paladin, F., Borro, M., Ricciardi, L., & Gangemi, S. (2023). Prevalence of Autoimmune and Autoinflammatory Diseases in Chronic Urticaria: Pathogenetic, Diagnostic and Therapeutic Implications. *Biomedicines*, *11*(2), 410. doi:10.3390/biomedicines11020410

Myers, M. G., Jr, Leibel, R. L., Seeley, R. J., & Schwartz, M. W. (2010). Obesity and leptin resistance: distinguishing cause from effect. *Trends in endocrinology and metabolism: TEM*, *21*(11), 643–651. doi:10.1016/j.tem.2010.08.002.

Nakamizo, S., Egawa, G., Miyachi, Y., & Kabashima, K. (2012). Cholinergic urticaria: pathogenesis-based categorization and its treatment options. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *26*(1), 114–116. doi:10.1111/j.1468-3083.2011.04017.x

Ng, S. W., & Popkin, B. M. (2012). Time use and physical activity: a shift away from movement across the globe. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *13*(8), 659–680. doi:10.1111/j.1467-789X.2011.00982.x

OECD. (2019). *The Heavy Burden of Obesity*. Paris: OECD Publishing.

Ombrello, M. J., Remmers, E. F., Sun, G., Freeman, A. F., Datta, S., Torabi-Parizi, P., … Milner, J. D. (2012). Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *The New England journal of medicine, 366*(4), 330–338. doi:10.1056/NEJMoa1102140

References (Cont.)

Oztop, N., Beyaz, S., & Orcen, C. (2022). Abdominal Obesity and Metabolic Parameters in Chronic Spontaneous Urticaria. *Med Bull Haseki, 60*, 263-269.

Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, F. X., & Eckel, R. H. (2006). Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arteriosclerosis, thrombosis, and vascular biology*, *26*(5), 968–976.doi:10.1161/01.ATV.0000216787.85457.f3

Popkin, B. M., & Slining, M. M. (2013). New dynamics in global obesity facing low- and middle-income countries. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *14 Suppl 2*(0 2), 11–20. doi:10.1111/obr.12102

Prashamsa, P., Null, B., & Rm, D.. (2020).Aquagenic Urticaria- Chronic Spontaneous Urticaria with Diagnostic Challenges. *Clinical and Experimental Pharmacology, 10*(4), 1-4.

Raison-Peyron, N., Reymann, V., & Bessis, D. (2017). Follicular Traction Urticaria: A New Form of Chronic Inducible Urticaria?. *Acta dermato-venereologica*, *97*(4), 522–523. doi:10.2340/00015555-2558

Ring, J. (2016). Chronic urticaria: new hope for an old disease. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *30 Suppl 5*, 3–4. doi:10.1111/jdv.13742

Robles-Tenorio, A., Tarango-Martinez, V. M., & Sierra-Silva, G. (2020). Aquagenic urticaria: Water, friend, or foe?. *Clinical case reports*, *8*(11), 2121–2124. doi:10.1002/ccr3.2880

Rujitharanawong, C., Tuchinda, P., Chularojanamontri, L., Nanchaipruek, Y., Jantanapornchai, N., Thamlikitkul, V., & Kulthanan, K. (2022). Natural history and clinical course of patients with dermographism in a tropical country: a questionnaire-based survey. *Asia Pacific allergy, 12*(4), e39. doi:10.5415/apallergy.2022.12.e39

References (Cont.)

Ryan, D., Tanno, L. K., Angier, E., Clark, E., Price, D., Zuberbier, T., & Maurer, M. (2022). Clinical review: The suggested management pathway for urticaria in primary care. *Clinical and translational allergy*, *12*(10), e12195. doi:10.1002/clt2.12195

Sakboonyarat, B., Pornpongsawad, C., Sangkool, T., Phanmanas, C., Kesonphaet, N., Tangthongtawi, N., … Rangsin, R. (2020). Trends, prevalence and associated factors of obesity among adults in a rural community in Thailand: serial cross-sectional surveys, 2012 and 2018. *BMC public health*, *20*(1), 850. doi:10.1186/s12889-020-09004-w

Salman, A., Porras, N.M. & Gimenez-Arnau, A. (2023). Acute and Chronic Urticaria Diagnosis and Management Taking into Account Their Differences. *Curr Treat Options Allergy, 10*(130–147). doi:10.1007/s40521-023-00333-w

Santa, C., Valente, C. L., Mesquita, M., Lopes, J., Cardoso, I., Rodrigues, J., … Lopes, I. (2022). Acute urticaria in children: from pediatric Emergency Department to allergology consultation at a Central Hospital. *European annals of allergy and clinical immunology, 54*(4), 168–174. doi:10.23822/EurAnnACI.1764-1489.204

Schauer, P. R., Bhatt, D. L., Kirwan, J. P., Wolski, K., Aminian, A., Brethauer, S. A., … STAMPEDE Investigators (2017). Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *The New England journal of medicine*, *376*(7), 641–651. doi:10.1056/NEJMoa1600869

Schettini, N., Corazza, M., Schenetti, C., Pacetti, L., & Borghi, A. (2023). Urticaria: A Narrative Overview of Differential Diagnosis. *Biomedicines, 11*(4), 1096. doi:10.3390/biomedicines11041096

Shalom, G., Magen, E., Babaev, M., Tiosano, S., Vardy, D. A., Linder, D., … Cohen, A. D. (2018). Chronic urticaria and the metabolic syndrome: a cross-sectional community-based study of 11 261 patients. *Journal of the European Academy of Dermatology and Venereology: JEADV, 32*(2), 276-281. doi:10.1111/jdv.14548

References (Cont.)

Sharma, A., Kumar, A., Jha, A., Agarwal, A., & Misra, A. (2020). The impact of obesity on inflammatory markers used in the assessment of disease activity in rheumatoid arthritis a cross-sectional study. *Reumatologia*, *58*(1), 9-14. doi:10.5114/reum.2020.93506

Shi, Y. Z., Cao, W., Li, C. X., Xiao, X. J., Huang, Y., Zhang, L. X., … Li, Y. (2022). Acupuncture and Related Therapies for Chronic Urticaria: A Critical Overview of Systematic Reviews. *Evidence-based complementary and alternative medicine : eCAM*, *2022*, 2094589. doi:10.1155/2022/2094589

Soria, A., Du-Thanh, A., Amsler, E., Raison-Peyron, N., Mathelier-Fusade, P., Staumont-Sallé, D., … French Urticaria Group (GUS) of French Dermatological Society (2018). Obesity is not associated with severe chronic urticaria in a French cohort. *Journal of the European Academy of Dermatology and Venereology: JEADV*, *32*(6), e247–e249. doi:10.1111/jdv.14767

Termeer, C., Staubach, P., Kurzen, H., Strömer, K., Ostendorf, R., & Maurer, M. (2015). Chronic spontaneous urticaria - a management pathway for patients with chronic spontaneous urticaria. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *13*(5), 419–428. doi:10.1111/ddg.12633

Tomaszewska, K., Słodka, A., Tarkowski, B., & Zalewska-Janowska, A. (2023). Neuro-Immuno-Psychological Aspects of Chronic Urticaria. *Journal of clinical medicine*, *12*(9), 3134. doi:10.3390/jcm12093134

Tuer, W. F., James, W. D., & Summers, R. J. (1986). Contact urticaria to O-phenylphenate. *Annals of allergy*, *56*(1), 19–21.

Vena, G. A., & Cassano, N. (2017). The link between chronic spontaneous urticaria and metabolic syndrome. *European annals of allergy and clinical immunology*, *49*(5), 208–212. doi:10.23822/EurAnnACI.1764-1489.12

References (Cont.)

Vergara-de-la-Campa, L., Gatica-Ortega, M. E., Pastor-Nieto, M. A., Molina-Figueras, E., Pérez-Mesonero, R., Luna-Bastante, L., … Giménez-Arnau, A. (2020). Vibratory urticaria-angioedema: further insights into the response patterns to vortex provocation test. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *34*(11), e699–e701. doi:10.1111/jdv.16396

Wang, Y., & Lim, H. (2012). The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. *International review of psychiatry (Abingdon, England)*, *24*(3), 176–188. doi:10.3109/09540261.2012.688195

Wedi, B., & Traidl, S. (2021). Anti-IgE for the Treatment of Chronic Urticaria. *ImmunoTargets and therapy*, *10*, 27–45. doi:10.2147/ITT.S261416

Westerterp, K. R. (2004). Diet induced thermogenesis. *Nutrition & metabolism*, *1*(1), 5. doi:10.1186/1743-7075-1-5.

WHO Expert Consultation (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet (London, England)*, *363*(9403), 157–163. doi:10.1016/S0140-6736(03) 15268-3

Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., … STEP 1 Study Group (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *The New England journal of medicine*, *384*(11), 989–1002. doi:10.1056/NEJMoa2032183

World Health Organization (WHO). (2020). *Obesity and overweight*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Yanase, Y., Matsubara, D., Takahagi, S., Tanaka, A., Ozawa, K., & Hide, M. (2023). Basophil Characteristics as a Marker of the Pathogenesis of Chronic Spontaneous Urticaria in Relation to the Coagulation and Complement Systems. *International journal of molecular sciences*, *24*(12), 10320. doi:10.3390/ijms2412103200

References (Cont.)

Yanase, Y., Takahagi, S., Ozawa, K., & Hide, M. (2021). The Role of Coagulation and Complement Factors for Mast Cell Activation in the Pathogenesis of Chronic Spontaneous Urticaria. *Cells*, *10*(7), 1759. doi:10.3390/cells10071759

Yang, X., Kong, M., Wang, H., Song, Z., & Chen, Q. (2023). Symptomatic dermographism induced by oral minocycline: A report of four cases. *The Journal of dermatology, 50*(8), 1063–1067. doi:10.1111/1346-8138.16779

Ye, Y. M., Jin, H. J., Hwang, E. K., Nam, Y. H., Kim, J. H., Shin, Y. S., & Park, H. S. (2013). Co-existence of chronic urticaria and metabolic syndrome: clinical implications. *Acta dermato-venereologica*, *93*(2), 156–160. https://doi.org/10.2340/00015555-1443

Yosipovitch, G., Biazus Soares, G., & Mahmoud, O. (2023). Current and Emerging Therapies for Chronic Spontaneous Urticaria: A Narrative Review. *Dermatology and therapy*, *13*(8), 1647–1660. doi:10.1007/s13555-023-00972-6

Yücel, M. B., Ertas, R., Türk, M., Muñoz, M., Atasoy, M., & Maurer, M. (2022). Food-dependent and food-exacerbated symptomatic dermographism: New variants of symptomatic dermographism. *The Journal of allergy and clinical immunology, 149*(2), 788–790. doi:10.1016/j.jaci.2021.07.030

Zaikov, S., Bogomolov, A. Y., Kyrylenko, T. V., & Gryshylo, A.. (2022). Acute Urticaria as a Current Multidisciplinary Problem. *Asthma and allergy,2022*(3). doi:10.31655/2307-3373-2022-3-66-76

Zbiciak-Nylec, M., Wcisło-Dziadecka, D., Kasprzyk, M., Kulig, A., Laszczak, J., Noworyta, M., … Brzoza, Z. (2018). Overweight and obesity may play a role in the pathogenesis of chronic spontaneous urticaria. *Clinical and Experimental Dermatology*, *43*(5), 525-528. doi:10.1111/ced.13368

Zhao, Z., Reimann, S., Wang, S., Wang, Y., & Zuberbier, T. (2019). Ordinary vibratory angioedema is not generally associated with ADGRE2 mutation. *The Journal of allergy and clinical immunology*, *143*(3), 1246–1248.e4. doi:10.1016/j.jaci.2018.10.049

References (Cont.)

Zhou, B., Li, J., Liu, R., Zhu, L., & Peng, C. (2022). The Role of Crosstalk of Immune Cells in Pathogenesis of Chronic Spontaneous Urticaria. *Frontiers in immunology*, *13*, 879754. doi:10.3389/fimmu.2022.879754

Zuberbier, T., Abdul Latiff, A. H., Abuzakouk, M., Aquilina, S., Asero, R., Baker, D., … Maurer, M. (2022). The international EAACI/GA²LEN/EuroGuiDerm /APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*, *77*(3), 734-766. doi:10.1111/all.15090

Zuberbier, T., Altrichter, S., Bauer, S., Brehler, R., Brockow, K., Dressler, C., … Maurer, M. (2023). S3 Guideline Urticaria. Part 1: Classification and diagnosis of urticaria - German-language adaptation of the international S3 Guideline. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *21*(1), 81–93. doi:10.1111/ddg.14906

Appendix

Case Record Form

Case No. : _____

CASE RECORD FORM

AGE : _____

SEX : ☐ male   ☐ female

Weight (kg) : _____   Height(cm) :_____   BMI(Kg/m²) :_____

Underlying disease : ☐ None
☐ Hypertension   ☐ DM   ☐ Dyslipidemia   ☐ Atopic dermatitis
☐ Allergic rhinitis   ☐ Asthma
☐ Thyroid disease   ☐ others :_____

Current medications : 1._____
2._____
3._____

Clinical information :
Symptoms :   ☐ wheals
☐ angioedema
☐ wheal and angioedema
☐ others : _____

Time of the symptoms (Pre-diagnosis) : _____ months _____ weeks

Lab investigations : (For work up cause)
☐ None

Lab result : (if any abnormal)
☐ CBC   ☐ normal   ☐ anemia   ☐ leukocytosis/leukopenia
☐ thrombocytopenia ☐ other :_____
☐ ESR   ☐ normal   ☐ ESR (+) :_____
☐ LFT   ☐ normal   ☐ hepatocellular injury (↑ AST/ALT)
☐ cholestasis (↑ ALP/GGT)
☐ ↓ albumin ☐ prolong PT
☐ ↑ bilirubin ☐ other :_____
☐ Hepatitis profile   ☐ normal   ☐ HBsAg(+) ☐ Anti-HBs(+)
☐ Anti-HBc(+) ☐ Anti-HAV
Interpret = _____
☐ ANA   ☐ normal   ☐ ANA (+) :_____
☐ UA   ☐ normal   ☐ abnormal :_____
☐ Stool exam   ☐ normal   ☐ abnormal :_____
☐ Chest X-ray   ☐ normal   ☐ abnormal :_____
☐ Thyroid function test   ☐ normal   ☐ other : _____
☐ hypothyroidism ☐ hyperthyroidism
☐ Thyroid antibodies   ☐ normal   ☐ ATPO* (+) ☐ ATA**(+)
☐ Others : _____   _____

☐ Skin biopsy (if any) : _____

*ATPO=antiperoxidase antibody, **ATA=antithyroglobulin antibody

RECORDER : _____
DATE :_____

Biography

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