INTRODUCTION

Urticaria is a condition characterized by the development of wheals (hives), angioedema, or both. Chronic Spontaneous Urticaria (CSU) Spontaneous appearance of wheals, angioedema or both for >6 weeks due to known cause e.g.(the presence of mast cell-activating autoantibodies) or unknown cause ***(Zuberbier et al., 2018).***

Urticaria activity Score (UAS) is a patient-reported outcome measure for patients with chronic spontaneous urticaria that includes 2 items: assesses the key sign (hives) and symptom (itch). Items are recorded individually, and the UAS7 is calculated as the summation of pruritus and number of hives over 1 week ***(Hollis et al., 2018)***. The international EAACI / GA²LEN/EDF/WAO guidelines for urticaria recommend the use of the UAS in clinical practice for assessing disease activity and response to medication in patients with chronic spontaneous urticaria (CSU**)** ***(Zuberbier et al., 2014).***

29% of chronic urticaria patients have metabolic syndrome with poor clinical outcomes for CU, such as a higher urticaria activity score (UAS) and uncontrolled CU. Most proinflammatory adipokines are overproduced in metabolic syndrome ***(Deng* and Scherer *2010).***

CU associated with an altered immune response related to chronic systemic inflammation ***(Grzanka et al., 2015).*** Low-grade inflammation can stimulate activation of mast cell upon the release of a lot of adipokines, including interleukin (IL)-6, IL-9, and IL-33 ***(Sismanopoulos et al., 2013).***

Leptin is one of the main cytokines derived from adipose tissue, not only regulates fat metabolism but also regulate many physiologic functions such as immune or pro inflammatory responses, high leptin levels may enhance T-helper (Th1) immune responses and increase pro-inflammatory cytokines production such as IL-6 and tumor necrosis factor (TNF) ***(Lee et al., 2018).***

AIM OF THE STUDY

The aim of this study is to evaluate leptin levels in patients with chronic spontaneous urticaria, to investigate the possible role of leptin in chronic spontaneous urticaria pathogenesis and to outline relationships between serum leptin and urticaria severity.

Chapter 1

CHRONIC URTICARIA

Introduction:

Urticaria is a common disease characterized by development of wheals (hives), angioedema, or both, with prevalence around 25% of the general population. It is classified into acute and chronic forms, the former affecting 20% of the general population and the latter up to 5%. (***Fine and Bernstein 2016)***

Definition

Urticaria is defined as the sudden development of transient hives (wheals) and angioedema or both ***(Radonjic-Hoesli et al., 2018)***.

Clinical appearance

Sudden appearance of wheals, angioedema, or both epitomizes Urticaria, with variations in durations, intervals and the overlap of their appearance defining the picture of the disease.

- **A wheal has three typical features:** ***fig.(1)***

1. Central swelling of variable size, surrounded by reactive erythema.

2. Itching or sometimes a burning sensation.

3. A fleeting nature, with the skin returning to its normal appearance, usually within 1–24 h, sometimes even quicker ***(Zuberbier et al., 2014).***

Figure (1): Urticarial wheals ***(Sussman et al., 2015).***

- **Angioedema is characterized by:** ***fig. (2)***

1. A sudden, pronounced erythematous or skin coloured swelling of the lower dermis and subcutis or mucous membranes,
2. Sometimes pain, rather than itch.
3. A resolution slower than that of wheals (can take up to 72 hours) ***(Zuberbier et al., 2018).***

In 10–20% of the cases, it may be the initial and often the only presentation of urticaria ***(Zuberbier et al., 2014).*** In addition to the skin and adjacent mucosa, the gut is typically affected by certain types of angioedema, e.g., hereditary angioedema. Angioedema of the pharynx or larynx may be so severe as to be life threatening by means of asphyxiation ***(Wu et al., 2016).*** Its resolution is less abrupt than wheals and can take up to 72 h.

Figure (2): Angioedema ***(Gold smith et al., 2011).***

Prevalence and epidemiology:

The prevalence of chronic urticaria in adults is estimated to be 0.5% to 5% ***(Bernstein et al., 2014).***

It affects females more than males (females 68-80% of cases) ***(Broder et al., 2015).***

CSU is the commonest subgroup of chronic urticaria, It has been determined that chronic spontaneous urticaria will

affect between 0.6% to 5% ***(Shin & Lee, 2017)*** of the general population during their lifetime.

Clinical Classification of Urticaria

Urticaria is classified according to both duration and the cause that triggers it ***(Zuberbier et al., 2018).***

It is classified into acute and chronic form.

1- Acute urticaria

It is defined as recurrent appearance of wheals with or without angioedema for less than 6 weeks.

2- Chronic urticaria:

It is recurrent appearance of wheals with or without angioedema for more than 6 weeks ***(Zuberbier et al., 2014).***

Classification of chronic urticaria subtypes (presenting with wheals, angioedema, or both)

Chronic urticaria can be classified into chronic inducible urticaria or chronic spontaneous urticarial (CSU) according to whether it is induced by a trigger or it occurs spontaneously ***(Magerl et al., 2016). (Table 1)***

Table (1): Chronic urticaria subtypes.

Chronic spontaneous urticaria	**Inducible urticaria**
Spontaneous appearance of wheals, angioedema, or both more than 6 weeks due to known or unknown causes	Symptomatic dermographism(urticaria factitia, dermographic urticaria) Cold urticaria Delayed pressure urticaria Solar urticaria Heat urticaria Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

(Zuberbier et al., 2014)

A-Chronic spontaneous urticaria:

It is the most abundant type of chronic urticaria ***(Umit et al., 2011).***

Chronic spontaneous urticarial is sometimes linked to other diseases such as obesity, anxiety, dissociative and somatoform disorders, and malignancies ***(Lapi et al., 2016).***

Two thirds of chronic spontaneous urticarial patients reacts to physical triggers ***(Sánchez et al., 2017)***.

It is considered a mast cell-driven disease triggered by infections, food or drug intolerance, activation of the

coagulation cascade, genetic disposition, or autoimmunity ***(Kolkhir et al., 2016).***

It can presented by both type I (IgE mediated) or type II (autoantibodies of IgG or IgM type) hypersensitivity reactions ***(Kolkhir et al., 2016)***.

More than 50% of chronic spontaneous urticarial cases are thought to be caused by an autoimmune mechanism. This is supported by the observation that 60% of patients with chronic spontaneous urticaria will develop a wheal and flare reaction to intradermal autologous serum injections in the autologous serum skin test (ASST) ***(ASST: intradermal injection of patients own serum) is often used as a screening test for autoimmune CSU since some studies found positive reactions more frequently in CSU patients compared with healthy controls, atopic individuals, or cholinergic urticaria (Kolkhir et al., 2016). Fig. (3)***

Figure (3): A positive autologous serum skin test. The serum induced wheal has a diameter ≥1.5 mm of the saline-induced wheal and the redness score =2 (compared with the histamine induced redness) at 30 min ***(Vohra et al., 2011).***

Chronic spontaneous urticaria can be represented by systemic signs and symptoms that are under-recognized in daily practice such as joint pain or swelling (55.3%), headache/fatigue (47.6%), flushing (42.7%), wheezing or breathlessness (30.1%), gastrointestinal complaints (26.2%), and palpitations (9.7%) ***(Doong et al., 2017)***.

B- Chronic Inducible Urticaria:

Chronic inducible urticaria is classified as physical inducible urticaria or non-physical inducible urticaria.

Physical inducible urticaria includes symptomatic dermographism/urticaria factitia, cold- and heat-induced urticarias, delayed pressure urticaria, solar urticaria, and vibratory angioedema ***(Magerl et al., 2016).***

Non-physical Chronic inducible urticarial include cholinergic urticaria, contact urticaria, and aquagenic urticaria ***(Magerl et al., 2016).***

Symptomatic Dermographism

It is the most frequent form of physical urticaria, It is an exaggerated response to a relatively minor stimulus as pressure, rubbing, or scratching, e.g., induced by trouser, and its wheals disappear within minutes after elimination of the causative stimulus ***(Mlynek et al., 2013).***

Acquired Cold Urticaria

It is the second most common type of physical urticaria, it is induced by exposure to cold air, liquids, or solids and occurs more frequently in women than men ***(Magerl et al., 2016).***

Heat-Induced Urticaria

It is a very rare variant of physical urticaria, a circumscribed wheal and flare reaction develops immediately when exposed to local heat to the skin. The wheals usually persist for 1–3 h ***(Abajian et al., 2014).***

Delayed Pressure Urticaria

Painful swellings, itching, or burning occur several hours after exposure to vertical pressure and may persist for hours, sometimes longer than 24 h. Triggers are carrying backpacks or bags with shoulder straps, sitting on hard chairs, tight shoes, carrying heavy bags by hand ***(Abajian et al., 2014).***

Solar Urticaria

It is rare type of physical urticaria, In this type the offending trigger is a UV-A light, while provocation by visible or UV-B light is less frequent ***(Du-Thanh et al., 2013).***

Cholinergic Urticaria

Cholinergic urticaria (ChU) is triggered by a sudden increase of body core temperature, e.g., induced by

exercise/exertion, fever, hot baths or showers, emotional stress, hot or spicy foods, and drinks. Its prevalence is higher in young adults and peaks in winter in some patients ***(Ramam and Pahwa 2012).***

Vibratory Angioedema

This extremely rare variant of physical urticaria typically presents with angioedema immediately developing after exposure to local vibration ***(Abajian et al., 2014)***.

Contact Urticaria

Upon contact with the provoking substance, contact urticaria immediately manifests with wheals that disappear within a few hours ***(Wedi and Kapp, 2006).***

Aquagenic Urticaria

Patients exhibit folliculocentric wheals of 1–3 mm diameter and surrounding larger flares within 20–30 min after skin contact to water, sweat, or tears ***(Rothbaum and McGee, 2016).***

Urticaria Impairs Quality of Life

For daily routine assessment of disease activity, the patients' health related quality of life and the disease impact on daily activities the Urticaria Activity Score (UAS) 7 is recommended which assesses the number of wheals and itch

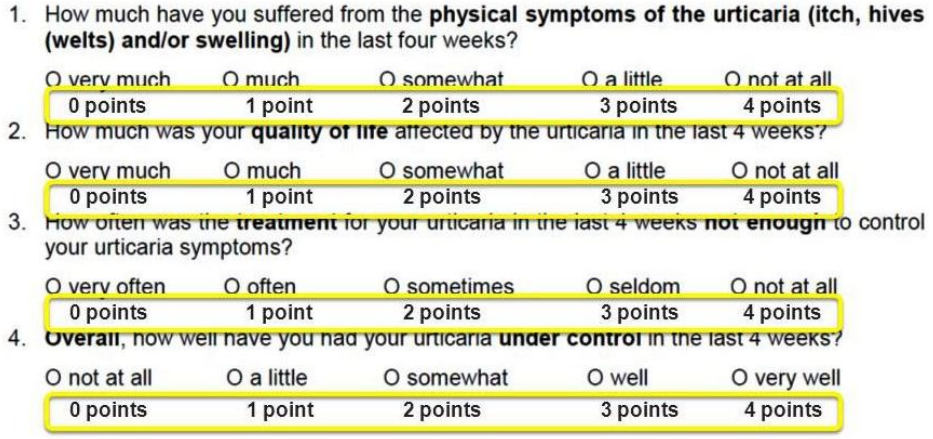
intensity on seven consecutive days (maximum score per day: six; zero = no symptoms, three = severe symptoms) ***Table (2).*** It correlates with the impact on quality of life, sleep and daily activity interference, presence of angioedema, and diphenhydramine use ***(Stull et al., 2017).***

Table (2): Urticaria activity score ***(Zuberbier et al., 2014).***

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6 for each day is summarized over one week (maximum 42).

Also urticaria can be assessed by urticaria control test (UCT) which can evaluate retrospectively the level of urticaria control over the past 4 weeks using four questionnaires ***(Weller et al., 2014). fig. (4)***



1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

O very much	O much	O somewhat	O a little	O not at all
0 points	1 point	2 points	3 points	4 points

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

O very much	O much	O somewhat	O a little	O not at all
0 points	1 point	2 points	3 points	4 points

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

O very often	O often	O sometimes	O seldom	O not at all
0 points	1 point	2 points	3 points	4 points

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

O not at all	O a little	O somewhat	O well	O very well
0 points	1 point	2 points	3 points	4 points

Figure (4): Urticaria control test ***(Weller et al., 2014).***

Pathogenesis

Although urticaria is a common disease, its pathogenesis is barely understood, and is probably characterized by many mechanisms, including autoimmunity, autoallergy, and inflamation ***(Bracken et al., 2019).***

Urticaria is a mast cell driven disease and its signs and symptoms develop when skin mast cells or basophils degranulate and release histamine and other proinflammatory mediators such as platelet-activating factor (PAF) and cytokines which results in sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment to urticarial lesions ***(Zuberbier et al., 2014).***

In chronic spontaneous urticaria, the degranulation of these cells in some patients is thought to be due to the effects of autoantibodies directed against a subunit of the high-affinity

IgE receptor, FcεRIa, or to IgE itself. Other mechanisms of mast cell or basophil activation that are potentially relevant to CSU involve autoantigens and IgE directed against these autoantigens, as well as complement components, cytokines and neuropeptides ***(Chang et al., 2015). Fig. (5).***

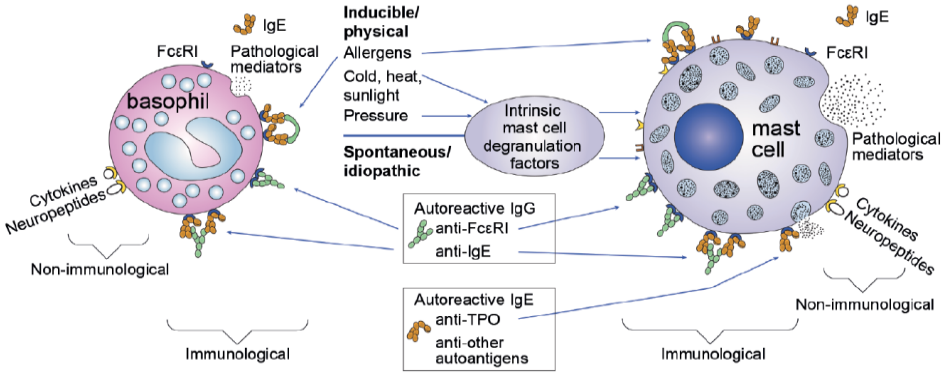


Figure (5): Pathogenesis of chronic urticaria (CU) ***(Beck et al., 2017).***

Autoreactivity/autoimmunity

The autoimmune pathogenesis hypothesis is supported by the detection of circulating autoreactive CD4+ T cells that proliferate in response to FcεRI in >50% of patients with chronic urticaria examined ***(Auyeung et al., 2016).***

These circulating functionally active IgG autoantibodies are directed against either the high-affinity IgE receptor (FcεRI) present on both mast cells and basophils (in most cases) or membrane-bound IgE (in a minority of patients) ***(Asero et al., 2017)***. ***fig.6***