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# Markers for the involvement of endothelial cells and the coagulation system in chronic urticaria: a systematic review.

Chronic urticaria and endothelial cell involvement

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**ABSTRACT**

Chronic urticaria (CU) is a chronic inflammatory mast cell-driven disorder. Endothelial cells (ECs)contribute importantly to key features of CU. Several markers of EC (dys)function in CU have been reported, but have not yet been systematically reviewed. In this study, we systematically reviewed and categorized all published markers of EC functions in CU through a comprehensive search in Pubmed, The Cochrane Library, Web of Science and SCOPUS using the following Mesh terms: chronic urticaria AND pathogenesis AND (vasculopathy OR microangiopathy OR endothelial cells OR marker). In total, 79 articles were selected and the identified biomarkers were categorized according to EC (dys)function in CU. The most frequent and consistently reported upregulated biomarkers in CU skin were adhesion molecules, TF and P-selectin. The most frequently reported upregulated and reliable biomarkers in sera of CU patients were F1+2 for coagulation cascade involvement, D-dimers for fibrinolysis and MMP-9 for vascular permeability. Emerging biomarkers described in the selected articles were endostatin, heat shock proteins, cleaved high molecular weight kininogen and adipokines. This systematic review contributes to the pool of growing evidence for vascular involvement in CU where EC dysfunction is present in different aspects of cell survival, maintenance of vascular structure and coagulation/fibrinolysis balance.

**KEYWORDS:** biomarker ; chronic urticaria ; coagulation and fibrinolysis ; endothelial cell ; vascular involvement

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**Most important abbreviations:**

ASST: autologous serum skin test

Auto-Ab: autoantibody

CIndU: chronic inducible urticaria

CSU: chronic spontaneous urticaria

CuZnSOD: copper-zinc dismutase

CU: chronic urticaria

DPU: delayed pressure urticaria

EC(s): endothelial cell(s)

F1+2: prothrombin fragment 1+2

hsp-70: heat shock protein 70

ICAM: intercellular adhesion molecule

MC(s): Mast cell(s)

MDA: malondialdehyde

MnSOD: manganese superoxide dismutase

RAGE: receptor for advanced glycation end product

ROS: reactive oxygen species

SCF: stem cell factor

SOD: superoxide dismutase

TF: tissue factor

TG2: transglutaminase 2

UAS: urticaria activity score(s)

VCAM: vascular adhesion molecule

VEGF: vascular endothelial growth factor

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## Introduction

Chronic urticaria (CU) is a chronic inflammatory skin disorder for which different pathogenic mechanisms have been described. CU is characterized bythe activation of skin mast cells (MCs) with subsequent degranulation and the release of histamine and other pro-inflammatory mediators. As a result, the endothelium gets activated resulting in vasodilation and extravasation, clinically visible as erythema and itchy wheals and/or angioedema, respectively(1). These symptoms of CU develop recurrently and resolve spontaneously. In the inducible forms of CU, i.e. chronic inducible urticaria (CIndU), the activation of skin MCs is induced by definite triggers, such as cold temperatures in cold urticaria or physical exercise in cholinergic urticaria. In contrast, MC-activation in the spontaneous forms of CU, i.e. chronic spontaneous urticaria (CSU), is unprompted and occurs spontaneously. Well-recognized activators of MCs in CSU include IgE directed to autoallergens such as thyroperoxidase or interleukin(IL)-24 as well as IgG/IgM autoantibodies (auto-Abs) directed against the high-affinity receptor of IgE, FcεRI(2).The activation of endothelial cells (ECs) is a key feature in CU and leads to increased skin blood flow,leakage of fluid into the skin, cellular infiltration and vascular remodelling(3).The wheals in patients with CSU are characterized by perivascular leukocytic infiltration of eosinophils, basophils, T cells and neutrophils. Eosinophils have also been described to be increased in non-lesional skin of CSU patients (4, 5). Interaction between these leukocytes and ECs includingtransendothelial migration,are highly dependent on the expression and function of cell adhesion molecules. ECs also play a major role in hemostasis.They regulate the activation of platelets and the coagulation cascade and they release pro-fibrinolytic molecules. CSU has been described to be linked to elevated plasma levels of markers of thrombin generation, which has been proposed to involve EC-derived tissue factor(6-9). Recently, the presence of new blood vessels in the skin of CSU patients and significantly more CD31-positive ECs in lesional vs non-lesional skin have been reported(10).Also, CSU patients with high numbers of cutaneous CD31+ ECs had higher rates of recurrent

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angioedema and vice versa(11). Finally, ECs interact with MCs through the production of stem cell factor (SCF) -the ligand for c-KIT receptor that acts as the main growth factor of MCs- to supportMC proliferation and differentiation(12, 13). In most histological studies, an increase of MCs in the skin of patients with CSU has been described (1, 4). Taken together, these findings underline the importance of ECs in CSU, as targets of the mediators released by MCs and infiltrating cells as well as contributors to the pathogenesis. In this systematic review, we aim to identify all published markers of EC (dys)functions in CU through a comprehensive search.

## Methods

### Rationale and search process

Ongoing research mainly focusses on the immunological aspects of CU. Nevertheless, it is well known that vascular leakage resulting in CU skin lesions is a direct effect of EC involvementand that ECs are important key players in several other pathological features of CU (3). Over the past years, many independent studies haveinvestigated EC functions in CU and their corresponding markers. Therefore, with this study, we aimed to provide a comprehensive and systematic review of these reported findings andinvestigate published dataon the (direct and indirect) roles and functions of ECs and their related biomarkers. Specifically, astructured search on Pubmed, The Cochrane Library, Web of Science and SCOPUS was performed without limitation on publication date to identify articles on CU pathogenesis and the role of ECs, using the following Medical subject heading (Mesh) terms: chronic urticaria AND pathogenesis AND (vasculopathy OR microangiopathy OR endothelial cells OR marker). Focus areas of the search consisted of ECactivation, vascular permeability, angiogenesis, coagulation and fibrinolysis and EC interactions with other (immune) cells.

The structured search was last updated on the first of April 2020. Details on search strategy are shown in supplementary file I.

### Search strategy

Figure I illustrates the search strategy performed in this systematic review (14). Two independent reviewers (YM and KDS) screened all articles, based on title, abstract and full-text level. All studies on the

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role of ECs in the pathogenesis of CU were included in the systematic review. Titles and abstracts selected by either one of the reviewers were included for further screening on full-text level. After thorough reading and evaluation of every selected full-text, final articles matching our research question, were withheld. Additionally, the reference lists of the selected full text articles were searched for supplementary papers by both independent reviewers. These additional articles went through the same selection process performed by the same two reviewers.Articles in languages other than English, Dutch, French and German were excluded. All study designs with the exception of editorials, single case reports, case series or reviews were included. Mostly observational studies were selected, of which the majority was evaluated to be of fair quality using the quality assessment tool for observational studies adapted from the national institute of health (NIH) (supplementary file II)(15).

**Results**

Supplementary file III summarizes all 79 selected manuscripts on biomarkers reflecting EC dysfunction described in CU pathogenesis. The selected articles were then sorted according to description of the EC (dys) function in CU, as shown in Table I: EC-activation, increased vascular permeability, angiogenesis, coagulation cascade and complement impairment, immune dysregulation and interaction with other cells. Since many of these functional pathways interact, some markers were categorized in more than one functional group.

*Adhesion molecules are upregulated in the lesional skin of CSU patients*

A total of 14 different markers of EC activation were investigated in 21studies in the skin and/or the blood of patients with CU (Table II). The majority of selected articlescovered adhesion molecules as biomarkers of ECactivation: E-selectin (16-23), intercellular adhesion molecule (ICAM) (16-25), P-selectin (18, 20, 21, 26-28), platelet endothelial cell adhesion molecule (PECAM) (10), vascular cell adhesion molecule (VCAM)(16-20, 22-24) and vascular endothelial (VE)-cadherin (29).

In the lesional skin of CU patients,three of three studies and five of six (observational) studies reported P-selectin (20, 21, 28) and E-selectin(16, 19-22) to be upregulated, respectively. ICAMs(16, 18-22, 25), VCAMs(16, 19, 20, 22) and PECAM (10)were reported to be upregulated in the skin lesions of CSU and/or delayed pressure urticaria (DPU) and/or symptomatic dermographism in six of eight, four of six, and one of one study, respectively. Fibronectin and iC3b were investigated and described to be upregulated in one

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study each(Table II)(25). Normal regulation of cluster of differentiation (CD)-40 and its ligand CD40L (30-32)were reported in CSU lesional and non-lesional skin in one study, respectively.

A total of 10 markers of EC activation were investigated in12 different studies in the blood of CSU and/or symptomatic dermographism patients (Table II)(18, 20, 24, 26, 30, 31, 33-36). In particular, P- and E-selectin were reported to be upregulated in two of four(20, 26)and one of two studies(18), respectively.VCAM and ICAM were upregulated in one of three studies each(24).

*Vascular permeability is increased in CU through different mechanisms*

Although many symptoms of urticaria are mediated primarily by the actions of histamine on H1 receptors on ECs (resulting in hives)(37), also other,histamine independent mechanisms seem to contribute to vascular leakage. In total,15different articles covering markers of increased vascular permeability were selected (Table III). In these articlesthreehistamine-independent mechanisms, with associated biomarkers,are proposedto contribute to increased extravasation in CU:

a) Extravasation due to the disruption of tight junctions/proteolysis

Matrix metalloproteinase 9 (MMP9) was reported to be upregulated in CU blood in four of four studies (38-41). Moreover, advanced glycation end products (AGE) (42), receptor for advanced glycation end products (RAGE)(43)were found to be downregulated in CU blood in one study each.For S100 calcium and zinc-binding protein A8/9/12 (S100A8/9/12)only one study reported an upregulation in the serum of CU patients (44) (Table III).

b) Extravasation due tooxidative stress causing tissue damage

Seven different studies reported on 14 different markers (Table III), with not more than four studies per marker(45-51). Most markers were only studied once. In the blood of CU patients, glutathione peroxidase (GSH-Px)(45-48) was downregulated or normally regulated in 2 of 4 studies each.In CU skin, one studyshows an upregulation of oxidative stress markers SOD, glutathione, malondialdehyde (MDA) and MnSOD(51).

c) Extravasation due to bradykinin

One recent study found cleaved high molecular weight kininogen (cHK), a marker for bradykinin production, elevated in sera of CSU patients compared to healthy controls (52).

*Markers of angiogenesis are upregulated in the lesional skin of CSU patients*

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In CSU skin lesions, three different markers were shown to be upregulated in three different studies (Table IV): transglutaminase 2 (TG2) (53), calcitonin gene-related peptide (cGRP)(54) and vascular endothelial growth factor (VEGF)(10, 55).

In CSU and/or DPU sera, 11 different markers were investigated in 9 different studies. TG2(53), VEGF(55, 56), endostatin (57), thrombospondin-1 (TSP-1) (57), substance P (58) and chitinase-3-like protein 1 (YKL-40)(59) were described upregulated whilst controversially, other studies (n=4) showed normal regulation of VEGF or VEGF1 and VEGF2(56, 60), vascular endothelial growth factor receptor (VEGFR)(56), substance P (61) and the urokinase-type plasminogen activator (u-PA)/plasminogen activator inhibitor-1 (PAI-1)/soluble receptor of urokinase-type plasminogen activator (suPAR)system (62).

*Markers of extrinsic coagulation pathway activation and fibrinolysis are upregulated in CU*

The involvement of the hemostatic system in immune-mediated inflammation is widelyreported. In total, 33different articles were selected forthis topic:

a) The involvement of the coagulation cascade, i.e the extrinsic coagulation pathwaybeing triggered by the exposure of plasma to tissue factor (TF), has been demonstrated in the pathogenesis of CSU by several observations(6-9).In total, 18 factors involved in theextrinsic coagulation pathway were described in 13 different selected articles (Table V)(6, 7, 9, 34, 35, 55, 63-69).Prothrombin fragment 1+2 (F1+2) was the most investigated marker which showed upregulation in CU serum in eight of nine selected articles(6, 7, 9, 34, 55, 63-66). Activated partial thromboplastin time (aPTT) and FVIIa were reported at normal serum titers in four of five(34, 35, 68, 69) and two of five(6, 34) selected articles, respectively.

b) There is more and more evidence for local inflammatory responses in the urticarial lesions promoting fibrin formation and fibrinolysis. This results in the increase of several markers offibrinolysis/anti-coagulation. The most frequently reported marker isD-dimer (6, 7, 9, 34, 64, 65, 67-74). It wasshown to be upregulated in C(S)U serum in 13 of 14 selected articles. Other markers of fibrinolysis were studied in only one or two studies each, where the majority was either upregulated or normally regulated (Table V).

c) Markers of blood platelet involvement described in the selected articles are shown in Table V (18, 20, 21, 26-28, 68, 75-77). In the lesional skin of CU patients, P-selectin was upregulated in three of threeselected studies. In one of threepublished studies, P-selectin was also found upregulated in

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non-lesional skin. As for markers in the sera of CU patients, all investigated markers yield inconsistent findings across studies.

The role of the complement system (CS) in the pathogenesis of CU has not been exhaustively investigated (Table V). Regulation of complement in CU sera wasfound inconsistent in4 different selected articles: C1 esterase inhibitor(35), C3(6), C4(6, 35), C5a(6, 35). C5a was found upregulated in CSU lesional skin in one study (78).

*ECimmune signature: upregulation of IL-6 and IL-4in skin and/or serum*

Although mostly articles on vascular abnormalities in CU were reviewed and selected, also the (direct or indirect) interaction between ECs with the immune system can contribute to the emergence or maintenance of CU endothelial dysfunction. In total,19different articles suggesting and discussing this interaction, were selected. Five differentcytokines were all shown to be upregulated in lesional and/or non-lesional CU skin in fourselected articles (5, 16, 17, 79): Tumor Necrosis Factor α (TNF-α) (5), interferon ɣ (IFN-ɣ)(16, 17), interleukin (IL)-3 (5), IL-4 (16, 17, 79) and IL-33 (79). In CU sera, eight different immunological biomarkers, mostly cytokines, important in this EC-immune system communication, were examined in 16 selected articles (Table VI)(19, 23, 24, 36, 46, 53, 60, 70, 80-87). IL-6 was found upregulated in CSU sera in seven of eightinvestigating articles. As for the other markers in CSU sera, mostly inconsistent results were foundin fewer studies (Table VI).

*EC interaction with other cells*

A total of 15different selected articles covered EC-interaction with other (immune-type) cells:MCs (through SCF) (53, 88), macrophages (through migration inhibitory factor (MIF))(89) and neutrophils. Described biomarkers of the latter interaction were IL-6 (36, 46, 53, 60, 70, 80-82), IL-18 (60, 83-85), TNF-α (5, 36, 53, 60, 86) and adipokines(36).

**Discussion**

This is the first systematic review on the role of EC in CU pathogenesis.The best researched and consistently upregulated biomarkers in CU skin were adhesion molecules, TF and P-selectin (Figure II). The most frequently upregulated and reliable biomarkers in sera of CU patients were F1+2 for coagulation cascade involvement, D-dimers for fibrinolysis and MMP-9 for vascular permeability (Figure III).

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Multiple significantly elevated EC-activation markers, but mostly adhesion molecules, in the skin of CU patients underline the involvement of EC-activation in CU pathogenesis. These adhesion molecules have been found upregulated in lesional and non-lesional CU skin(17, 20-22). This suggests an endothelial involvement that is not only reactional but also continuous, where the EC maintains a latent minimal persistent inflammation status. In this state,adhesion moleculeslikely spread through blood vessels from the primary whealing site, possibly promoting the induction ofnew wheals. This diffusion might explain increased serum levels of such molecules in CU(18). Nevertheless, contradictory results were reported in the literature for ICAM, VCAM, E-selectin and P-selectin, which were not always found upregulated in CU sera(Table II) (18, 20, 24, 26, 27).

The endothelium also plays a critical role in controlling the passage of fluid into the tissue and influencing cellular trafficking (3). In CU skin, endothelium dysfunction is suggested to increase vascular permeability, with a consequent pro-inflammatory response. In total,15articles in our selection cover markers of vascular permeability. Although many symptoms of urticaria are mediated primarily by the actions of histamine on H1 receptors on ECs (resulting in hives)(37), other, mostly histamine-independentmechanisms described in several selected manuscripts, seem to contribute to vascular leakage (Table III). A first mechanism implies vascular leakage by disruption of tight junctions/proteolysis. The soluble forms of advanced glycation end products (AGE) and receptor for advanced glycation end products (RAGE)(42, 43) prevent receptor-mediated signaling by neutralization/removal of the pro-inflammatory ligands, this way functioning as an anti-inflammatory feedback mechanism.Soluble RAGE (sRAGE) consists of several forms, including endogenous secretory RAGE, which is a spliced variant of RAGE, and a shedded form derived from cell-surface RAGE. These forms of soluble RAGE, which carry all of the extracellular domains but are devoid of the transmembrane and intracytoplasmic domains, bind ligands including AGE and can antagonize RAGE signaling *in vitro* and *in vivo*(90-92). Furthermore, it was shown thatsRAGE preventsangiotensin II (Ang II)-induced VE-cadherin disruption in human umbilical endothelial cells. By doing so,sRAGE further attenuates the Ang II increased endothelial barrier permeability. Blockade or decrease of RAGE signaling by sRAGE attenuates Ang II-induced endothelial barrier permeability, indicatinga therapeutic potential of sRAGE in controlling vascular permeability under pathological conditions. In CU sera, a decrease of these molecules has been found, enhancing a pro inflammatory status and cellular dysfunction resulting in increased vascular permeability and recruitment of leukocytes to sites of inflammation.Additionally, a recent study hypothesizedthat enhanced vascular permeability and vasodilation in CSU may involvea different mechanism, i.e. through bradykinin release (52). In this study, cHK, a marker for bradykinin production,

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was elevated in CSU patients compared to healthy controls. Moreover, the observed increases in cHK levels were comparable to previously determined levels in hereditary angioedema type 1 and 2. Increased cHK was not limited to CSU patients with angioedema and was not associated with antihistamine responsiveness. In ECs, activation of bradykinin receptor-2 (B2R) by bradykinin induces the release of NO, prostacyclin, endothelium-derived hyperpolarizing factor, and t-PA, which exert diverse physiological actions on the cardiovascular system,including regulation of vascular tone, coagulation, fibrinolysis, and water–electrolyte balance(93).Nevertheless, one study showed downregulation of t-PA in sera of CSU patients (6).

The results of our review demonstrate that MMP-9 can be upregulated in the sera of CU patients and that this is associated with disease severity(38-41). MMP-9 is a zinc-dependent endopeptidaseresponsible for tissue remodeling and degradation of the extracellular matrix (94). Moreover,there is evidence that the presence of MMPs leads to increased vascular permeability, primarily through tight junction rearrangement by a mechanism involving VEGF (95).Also, oxidative stress causing tissue damage and angiogenesis are put forward as possible mechanisms for vascular leakage. Indeed, there is growing evidence that ROS can cause endothelial dysfunction and increased vascular permeability (96, 97). Unfortunately, in sera of CU patients, markers have been controversially found upregulated or downregulated. On the contrary, for CU skin, the literature clearly supports anupregulation of markers of oxidative stress causing tissue damage and angiogenesis (Table III and IV). The latter is shown by a significant upregulation of TG2 and VEGF. These findings shed light on histamine-independent mechanisms involved in vascular leakage in CU. Indeed,VEGF is the most potent direct-acting regulator of angiogenesis, and its expression is often excessive in chronic inflammatory diseases. VEGF induces proliferation, migration and tube formation of ECs. It promotes the secretion of MMPs and the expression of chemokines, as well as leukocyte adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin(98, 99).TG2 is the most widely distributed transglutaminase among tissue and cell types in humans. It is suggested as a marker of angiogenesis because of its involvement in maintaining tube formation through VEGF signalling (100).

Additionally, ECs also interact with the coagulation system in CU patients. Increased amounts of F1+2, a specific marker of activation of the extrinsic coagulation cascade, have been found in the sera of CU patients(6, 7, 9, 34, 55, 63-66). TF-expressing cells such as eosinophils and ECs are expanded in the skin of CSU patients and have shown to play a role in the activation of the extrinsic coagulation pathway. Enhanced expression of TF on ECs was found to be synergistically increased by the activation of toll-like receptors and histamine H1 receptors. The activation of this coagulation pathway may induce plasma

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extravasation followed by degranulation of skin MCs in CSU (101, 102). Nevertheless, the implication of a prothrombotic state in CU patients is still under debate since both depressed coagulation activity and normal plasma coagulation factors have also been reported (Table V). Nevertheless, in sera of CU patients, markers of fibrinolysis or anti-coagulation are clearly upregulated (6, 7, 9, 34, 64, 65, 67-73).

Although there is not a lot of data on TF in CU sera (6), it is clearly shown to be upregulated in CU skin in multiple selected articles (7-9), postulating tissue damage. Nevertheless, markers of ECinjury or apoptosis as described in other chronic (autoimmune) inflammatory diseases, have not been examined yet in CU skin. Since there is evidence for disease-driving auto-Abs in certain types of CU, it would be interesting to look for anti-endothelial cell antibodies (AECA), microparticles (MPs) or complement membrane attack complex (MAC) in CU serum and/or skin.

Evidence of a link between ECs, inflammation and hemostasis involves also many other (immune) cells and hemostatic proteins such as platelets and vWF respectively. The latter is a protein that links platelets to subendothelial components during vascular injury. In earlier studies, vWF was reported to be a marker of inflammation, being acutely released by activated endothelium. In addition, vWF was shown to be involved in the expression of P-selectin on leukocytes and therefore to recruit them to inflammatory sites either by directly binding them or by involving platelets in this process (103). In our selected articles controversial data was presented concerning the presence of markers of blood platelet activation in CU sera. Nevertheless, in CU skin, a clear upregulation of P-selectin was shown (Table V). As P-selectin is present both within ECs and platelets, there has been considerable debate whether or not raised plasma levels of soluble P-selectin reflect EC dysfunction, platelet activation or both. However, despite many conflicting reports the leading view is that soluble P-selectin does indeed reflect a certain aspect of platelet function or activity (26, 104, 105).

Although the immune system plays its own particular part in CU pathogenesis, its interaction with EC and therefore its role in vascular involvement, is not negligible. IL-6, one of the most often described cytokines in the selected articles, is consistently increased in sera of CU patients (36, 46, 53, 70, 80-82). It is a multifunctional pro-inflammatory, anti-apoptotic cytokine with an important role in the regulation of immune responses(106). The main effect of IL-6 is the proliferation and differentiation of cells(107). Abnormal IL-6 levels have been implicated in autoimmune diseases and chronic inflammatory processes(108). During the innate immune response, IL-6 favors T-cell development, maturation, and proliferation-inducing mononuclear cell accumulation, which in turn leads to a continuous secretion of the cytokine(109). Also, it is shown that IL-6 is capable of increasing endothelium permeability *in vitro*(110).Furthermore, IL-4 which was shown to be upregulated in CSU skin in three of three selected

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studies and in CSU serum in one of two selected studies, promotes the upregulation of VCAM-1 on the vascular endothelium, which in turn is necessary for eosinophil entry. Furthermore, it participates in basophil-EC communication through the STAT-6 dependent expression of CCL24 from endothelial cells leading to extravasation of eosinophils into the tissues (111, 112).

Moreover, there is also (limited) evidence of EC interaction with other inflammatory cells such as MCs. It is known for ECs to interact with MCs through the production of stem cell factor (SCF; c-kit ligand) to influence theirdevelopment and maturation. SCF is the only cytokine/growth factor that induces mediator release from human MCs(12, 13). Although histopathologic studies on urticaria showed an increased number of MCs in the dermis of both lesional and non-lesional CSU skin, Asero et al were not able to show SCF as a possible pathogenic factor in CU (88). In their study, serum SCF levels of all chronic inducible urticaria did not differ significantly from those found in healthy controls. Nevertheless, Hong et al found significantly increased MC surface marker c-kit in the lesional skin of patients with CSU compared to healthy controls (53).

Furthermore,our collected data provides limited evidence for EC interaction with macrophages.ECs produce MIF, which can serve as a macrophage activator(113). MIF-stimulated macrophages are functionally more active with regard to cell metabolism, adherence, ruffled membrane motility and spreading. Macrophages expressing the MIF receptor have been shown to function as accessory cells in the induction of T helper cells (114). Czarnetzki et al show increased expression of MIF on ECs in CU skin sections. In this study, authors suggest that this way ECs may aid in limiting the extent and duration of the disease by preventing macrophage immigration or by stimulating MIF expression and activation of macrophages to modulate the local immune response (89).

ECs interact with neutrophils, through cytokines such as IL-6(36, 46, 53, 60, 70, 80-82), IL-18 (60, 83-85), TNF-α (5, 36, 53, 60, 86), and adipokines(115-118)(119, 120). The latter is a relatively new discovery, which involves a new type of cytokine, this way expanding the spectrum of vascular involvement in CU pathogenesis. After all, it has been demonstrated that 30% of CU patients have metabolic syndrome. Most pro-inflammatory adipokines are overproduced in metabolic syndrome, while anti-inflammatory adipokines are downregulated, suggesting a possible relationship between adipokines and CU pathogenesis (115-118). Trinh et al. were the first to show a clear imbalance in pro-and anti-inflammatory adipokines in CU patients. Lipocalin-2 is a pro-inflammatory adipokine released from neutrophils upon stimulation with the potential of inducing endothelial dysregulation. It has shown to be significantly increased in sera of CU patients. Adiponectin, an anti-inflammatory adipokine, was shown significantly decreased in sera of CU patients (36).

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This systematic review summarizes the role of ECs in CU pathogenesis and its dysfunctional characteristics in different aspects of cell survival (activation and injury), maintenance of vascular structure and coagulation/fibrinolysis balance. It emphasizes a clear activation of ECs, upregulation of extrinsic coagulation pathway as well as fibrinolysis mechanisms. Importantly, our study exposed several gaps of knowledge, unmet needs in the field and controversies that require further data. The areas of need for further research on the role of endothelial cells in the pathogenesis include the mechanisms of EC-MC interaction, complement involvement, the role of the bradykinin system and other histamine-independent mechanisms in vascular permeability, the crosstalk of macrophages and EC and the role of newly discovered adipokines.

**Conclusion**

Although the etiology of CU remains unclear, this systematic review summarizes the important role of ECs in the pathogenesis of CU, a disease held to be driven by autoimmune mechanisms of MC activation. This review contributes to the pool of growing evidence for vascular involvement where EC dysfunction is present and prominent in different aspects of cell survival (activation and injury), maintenance of vascular structure and coagulation/fibrinolysis balance and where disturbed interactions between ECs and various other cells contribute to endothelial dysfunction.

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**APPENDICES**

**Table I. Studies on endothelial (dys)functions in chronic urticaria**

*Table legend: data are given as the number of articles selected in this systematic review, categorized according to EC (dys)function. Some articles covered more than one topic and were therefore categorized into more than one functional group. This way the grand total exceeds 79 articles.*

**Table II. Markers of EC-activation in chronic urticaria**

*Table legend: data are given as the number of selected articles describing significant upregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of EC adhesion molecules in CU. There was no*

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*downregulation described in any of the selected articles. Selected basic science articles (i.e. (partly) in vitro experiments) involving the process of EC adhesion and transendothelial migration of leukocytes are not included in this table.*

**Table III. Markers of vascular permeability in chronic urticaria**

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of vascular permeability in CU.*

**Table IV. Markers of angiogenesis and their regulation in chronic urticaria**

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of angiogenesis in CU.*

**Table V. Markers of the coagulation cascade and complement system in chronic urticaria**

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of the coagulation cascade and complement systemin CU. *no significant difference between CU and other types of urticaria; **no HC group, elevated DD-dimers in 48% of CSU patients; *** no HC group, elevated DD-dimers in 33% of CSU patients; ****not specified if statistically significant increase and no data given to extract a clear conclusion.*

**Table VI. Described cytokines/chemokines as markers of EC-immune system communication.**

*Table legend: data are given as the number of selected clinical articles describing upregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) in CU or certain CU subtypes, of markers of EC-immune system communication. There was no described downregulation of markers in any of the selected articles. Basic science articles investigating the process of this interaction in vitro are not included in this table..*

**Figure I.Flow diagram of search process according to PRISMA 2009 guidelines**

**Figure II. Summary of the main immunologic, hematologic and biochemical parameters studied in the skin of CU patients.**

*Abbreviations used in figure: C5a: complement C5a; CD: cluster of differentiation; CD40L: cluster of differentiation 40 ligand; cGRP: calcitonine gene-related peptide; CU: chronic urticaria; CuZnSOD: copper-zinc dismutase; E-sel: E-selectin; EC: endothelial cell; FVIII: Factor VIII; ICAM: intercellular adhesion molecule; iC3b: Inactivated complement 3b; IL-: interleukin-; IFN-ɣ: interferon gamma; TNF-α: tumor necrosis factor alpha; MDA: malondialdehyde; MIF: migration inhibitory factor; MnSOD: manganese superoxide dismutase; PECAM: platelet endothelial cell adhesion molecule; P-sel: P-selectin; SCF: stem cell factor; SOD: superoxide dismutase; TF: tissue factor; TG2: transglutaminase 2; VCAM: vascular adhesion molecule; VE: vascular endothelial; VEGF: vascular endothelial growth factor.*
*Doublesided arrow: coming from or going to endothelial cells, autofeedback loops possible*

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**Figure III. Summary of the main immunologic, hematologic and biochemical parameters studied in the serum of CU patients.**

*Abbreviations used in figure: AGE: advanced glycation end products; aPTT: activated partial thromboplastin time; α2- APL: α2-antiplasmin; AT III: antithrombin; C3: complement C3; C4: complement C4; C5a: complement C5a; CCL: chemokine (C-C) ligand; CD: cluster of differentiation; CD40L: cluster of differentiation 40 ligand; cHK: cleaved high molecular weight kininogen; CuZnSOD: copper-zinc dismutase; Cu: copper; CU: chronic urticaria; EC(s): endothelial cell(s);F1+2: prothrombin fragment 1+2; FI: factor I; FII: factor II; FV: Factor V; FVIII: factor VIII; FIX: factor IX; FX: factor X; FXI: factor XI; FXII: factor XII; FVIIa: activated factor VII; FDP: fibrin degradation products; GSH-Px: glutathione peroxidase; HMWK: high molecular weight kininogen; hsp-70: heat shock protein 70; ICAM: intercellular adhesion molecule; IFN-ɣ: interferon gamma; IL-: interleukin-;MDA: malondialdehyde; MMP: matrix metalloproteinases; MnSOD: manganese superoxide dismutase; MPV: mean platelet volume; PAI-1: plasminogen activator inhibitor-1;PDW: platelet distribution width; PT: prothrombin time; PUFA: plasma phospholipid fatty acid; P2Y12: adenosine diphosphate chemoreceptor;RAGE: receptor for advanced glycation end product; ROS: reactive oxygen species; SCF: stem cell factor; SFMC: soluble fibrin monomer complex; SOD: superoxide dismutase; suPAR Ag: soluble urokinase-type plasminogen activatorreceptor antigen;S100A8/9/12: S100 calcium and zinc-binding protein A8/9/12; TAS: total anti-oxidant status; TAT: thombin-antithrombin complex; TF: tissue factor; TFPI/Xa: tissue factor pathway inhibitor/activated factor Xa; TG2: transglutaminase 2; TM: thrombomodulin; TNF-α: tumor necrosis factor alpha; TOS: total oxidant status; t-PA: tissue-type plasminogen activator; TSP-1: thrombospondin-1; TT: thrombin time; u-PA Ag: urokinase-type plasminogen activatorantigen; VCAM: vascular adhesion molecule; VE: vascular endothelial;VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; Vit E: vitamin E;VWF:Ag: von Willebrand factor antigen; YKL-40: chitinase-3-like protein 1; Zn: zinc.*

*Striped arrow: produced by the cell from which the arrow parts; double sided arrow: coming from or going to endothelial cells, autofeedback loops possible*

**Supplementary file I. Details on search strategy using the Prisma 2009 checklist(12)**

**Supplementary file II. Quality assessment (QA) of the selected articles using the QA tool for observational studies adapted from the national institute of health**

**Supplementary file III. Summary of all 79 selected articles**

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**Table I. Studies on endothelial (dys)functions in chronic urticaria**

| **EC function** | **TOTAL** |
|---|---|
| EC activation | **21** |
| Vascular permeability | **15** |
| < intercellular junction disruption | 7 |
| < oxidative stress | 7 |
| < bradykinin-induced vasodilation | 1 |
| Angiogenesis | **10** |
| Coagulation cascade and complement impairment | **32** |
| Immune dysregulation | **19** |
| Interaction with other cells: mast cells, macrophages, neutrophiles | **15** |
| **GRAND TOTAL** | **112** |

*Table legend: data are given as the number of articles selected in this systematic review, categorized according to EC (dys)function. Some articles covered more than one topic and were therefore categorized into more than one functional group. This way the grand total exceeds 79 articles. Abbreviations used in table: EC: endothelial cell*

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| Markers in CU skin | Upregulation | Normal regulation | L/NL skin | Type of CU | TOTAL |
|---|---|---|---|---|---|
| P-selectin | Miyazaki et al (26) | | L | NS | 3 |
| | Haas et al (19) | | L | ChU, CoU | |
| | Zuberbier et al (18) | | L and NL | SD, CSU | |
| E-selectin | Haas et al (19) | | L and NL | CSU, DPU | 6 |
| | Zuberbier et al (18) | | L and NL | SD, CSU | |
| | Barlow et al (20) | | L and NL | DPU, CSU | |
| | Caproni et al (17) | | L | CSU | |
| | Caproni et al (14) | | L and NL | CSU | |
| | | Caproni et al (15) | L | CSU | |
| ICAM | Haas et al (19) | | L and NL | CSU, DPU | 8 |
| | Zuberbier et al (18) | | L and NL | SD, CSU | |
| | Barlow et al (20) | | L and NL | DPU, CSU | |
| | Caproni et al (17) | | L | CSU | |
| | Caproni et al (14) | | L and NL | CSU | |
| | Caproni et al (15) | | NL | CSU | |
| | Haas et al (23) | | L and NL | DPU, CSU | |
| | | Caproni et al (15) | L | CSU | |
| VCAM | Zuberbier et al (18) | | L and NL | SD, CSU | 6 |
| | Barlow et al (20) | | L | DPU, CSU | |
| | Caproni et al (17) | | L | CSU | |
| | Caproni et al (14) | | L and NL | CSU | |

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| | | | | | |
|---|---|---|---|---|---|
| | Caproni et al (15) | | NL | CSU | |
| | | Caproni et al (15) | L | CSU | |
| PECAM | Kay et al (10) | | L and NL | CSU | 1 |
| Fibronectin | Haas et al (22) | | L and NL | DPU, CSU | 1 |
| iC3b | Haas et al (23) | | L and NL | DPU, CSU | 1 |
| CD40 | | Hermes et al (30) | L and NL | CSU | 1 |
| CD40L | | Hermes et al (30) | L and NL | CSU | 1 |
| **GRAND TOTAL** | **23** | **5** | **NA** | **NA** | **28** |
| **Markers in CU serum** | **Upregulation** | **Normal regulation** | **L/N skin** | **Type of CU** | **TOTAL** |
| VE cadherin | Chen et al (27) | | NA | CSU | 1 |
| VCAM | Puxeddu et al (22) | | NA | CSU | 3 |
| | | Zuberbier et al (18) | NA | SD, CSU | |
| | | Caproni et al (16) | NA | CSU | |
| ICAM | Puxeddu et al (22) | | NA | CSU | 3 |
| | | Zuberbier et al (18) | NA | SD, CSU | |
| | | Caproni et al (16) | NA | CSU | |
| E-selectin | Caproni et al (16) | | NA | CSU | 2 |
| | | Zuberbier et al (18) | NA | SD, CSU | |
| P-selectin | Zuberbier et al (18) | | NA | SD, CSU | 4 |
| | Chandrashekar et al (24) | | NA | CSU | |
| | | Caproni et al (16) | NA | CSU | |

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| | | | | | |
|---|---|---|---|---|---|
| | | Palikhe et al (25) | NA | CSU | |
| CD-40L | Szegedi et al (29) | | NA | CSU | 2 |
| | | Jasinska et al (28) | NA | CSU | |
| CCL17 | Zhang et al (31) | | NA | CSU | 1 |
| CCL5 | Puxeddu et al (22) | | NA | CSU | 1 |
| TSP-1 | Puxeddu et al (54) | | NA | CSU | 1 |
| FVIII | Bork et al (33) | | NA | NS | 2 |
| | | Takeda et al (32) | NA | CSU | |
| **GRAND TOTAL** | **12** | **9** | **NA** | **NA** | **20** |

*Table legend: data are given as the number of selected articles describing significant upregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of EC adhesion molecules in CU. There was no downregulation described in any of the selected articles. Selected basic science articles (i.e. (partly) in vitro experiments) involving the process of EC adhesion and transendothelial migration of leukocytes are not included in this table. Abbreviations used in table:* CCL: chemokine (C-C) ligand; CD: cluster of differentiation; CD40L: cluster of differentiation 40 ligand; ChU: cholinergic urticaria; CoU: cold urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; DPU: delayed pressure urticaria; EC: endothelial cell; FVIII: Factor VIII; ICAM: intercellular adhesion molecule; iC3b: Inactivated complement 3b; L: lesional; NA: not applicable; NL: non-lesional; NS: not specified; PECAM: platelet endothelial cell adhesion molecule; SD: symptomatic dermographism; TSP-1: thrombospondin-1; U: urticaria; VCAM: vascular adhesion molecule; VE: vascular endothelial

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| Mechanisms of vascular permeability | Markers in CU skin | Upregulation | Downregulation | Normal regulation | Type of CU | TOTAL |
|---|---|---|---|---|---|---|
| Oxidative stress | SOD | Raho et al (48) | | | CSU | 1 |
| | Glutatione | Raho et al (48) | | | CSU | 1 |
| | MDA | Raho et al (48) | | | CSU | 1 |
| | Mn-SOD | Raho et al (48) | | | CSU | 1 |
| | CuZnSOD | | Raho et al (48) | | CSU | 1 |
| | **GRAND TOTAL** | **4** | **1** | **0** | **NA** | **5** |
| **Mechanisms of vascular permeability** | **Markers in CU serum** | **Upregulation** | **Downregulation** | **Normal regulation** | **Type of CU** | **TOTAL** |
| Intercellular junction disruption | RAGE | | Kasperska-zajac et al (40) | | CSU | 1 |
| | AGE | | Grzanka et al (39) | | CSU | 1 |
| | MMP-9 | Tedeschi et al (35)<br>Dilek et al (36)<br>Altrichter et al (37)<br>Kessel et al (38) | | | CSU<br>CSU<br>CSU<br>CSU | 4 |
| | S100A8/9/12 | Zhou et al (41) | | | CSU | 1 |
| | TOS | Dilek et al (46) | | | CSU | 1 |
| | TAS | | Dilek et al (46) | | CSU | 1 |
| | ROS | Cassano et al (47) | | | CSU | 1 |
| | SOD | Cassano et al (47) | | | CSU | 3 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Oxidative stress** | | Briganti et al (44) | | | CIU | |
| | | | Rajappa et al (43) | | CSU | |
| | MDA | Rajappa et al (43) | | Sagdic et al (45) | CSU | 3 |
| | | | | Kasperska-zajac et al (42) | CSU | |
| | GSH-Px | | Rajappa et al (43) | | CSU | 4 |
| | | | Briganti et al (44) | | CIU | |
| | | | | Sagdic et al (45) | CSU | |
| | | | | Kasperska-zajac et al (42) | CSU | |
| | Cu | Sagdic et al (45) | | | CSU | 1 |
| | Zn | | | Sagdic et al (45) | CSU | 1 |
| | CuZnSOD | | Sagdic et al (45) | Kasperska-zajac et al (42) | CSU | 2 |
| | MnSOD | | | Kasperska-zajac et al (42) | CSU | 1 |
| | Catalase | | Briganti et al (44) | | CIU | 2 |
| | | | | Kasperska-zajac et al (42) | CSU | |
| | Vit E | | Briganti et al (44) | | CIU | 1 |
| | PUFA | | | Briganti et al (44) | CIU | 1 |
| **Bradykinin-induced vasodilation** | cHK | Hofman et al (49) | | | CSU | 1 |
| | **GRAND TOTAL** | **12** | **9** | **9** | **NA** | **30** |

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of vascular permeability in CU. Abbreviations used in table: AGE: advanced glycation end products; cHK: cleaved high molecular weight kininogen; CIU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; Cu: copper; CU: chronic urticaria; CuZnSOD: copper-zinc dismutase; DPU: delayed pressure urticaria; GSH-Px: glutathione peroxidase; L: lesional; MDA: malondialdehyde; MMP: matrix metalloproteinases; MnSOD: manganese superoxide dismutase; NL: non-lesional; PUFA: plasma*

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*phospholipid fatty acid; RAGE: receptor for advanced glycation end product; ROS: reactive oxygen species; SOD: superoxide dismutase; S100A8/9/12: S100 calcium and zinc-binding protein A8/9/12; TAS: total anti-oxidant status; TOS: total oxidant status; Vit E: vitamin E; Zn: zinc*

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**Table IV. Markers of angiogenesis and their regulation in chronic urticaria**

| **Markers in CU skin** | **Upregulation** | **Normal regulation** | **L/NL skin** | **CU type** | **TOTAL** |
|---|---|---|---|---|---|
| TG2 | Hong et al (50) | | L | CSU | 1 |
| VEGF | Kay et al (10)<br>Tedeschi et al (52) | | L<br>L | CSU<br>CSU | 2 |
| cGRP | Kay et al (10) | | L | CSU | 1 |
| **GRAND TOTAL** | **4** | **0** | | **NA** | **4** |
| **Markers in CU serum** | **Upregulation** | **Normal regulation** | **L/NL skin** | **CU type** | **TOTAL** |
| TG2 | Hong et al (50) | | NA | CSU | 1 |
| VEGF | Jagodzinska et al (53)<br>Tedeschi et al (52) | | NA | DPU<br>CSU | 4 |
| | | Metz et al (57)<br>Jagodzinska et al (53) | NA | CSU<br>CSU | |
| VEGFR-1 | | Jagodzinska et al (53) | NA | CSU | 1 |
| VEGFR-2 | | Jagodzinska et al (53) | NA | CSU | 1 |
| Endostatin | Puxeddu et al (54) | | NA | CSU | 1 |
| TSP-1 | Puxeddu et al (54) | | NA | CSU | 1 |
| Substance P | Metz et al (57) | | NA | CSU | 2 |
| | | Tedeschi et al (58) | NA | CSU | |
| YKL-40 | Zhou et al (56) | | NA | CSU | 1 |
| u-PA antigen<br>suPAR antigen<br>PAI-1 activity | | Kasperska-zajac et al (59) | NA | CSU | 1 |
| **GRAND TOTAL** | **7** | **6** | **NA** | **NA** | **13** |

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of angiogenesis in CU. Abbreviations used in table: cGRP: calcitonine gene-related peptide; CSU: chronic spontaneous urticaria; CU: chronic urticaria; DPU: delayed pressure urticaria; L: lesional; NL: non-lesional; PAI-1: plasminogen activator inhibitor-1; suPAR: soluble receptor of urokinase-type plasminogen activator; TG2: transglutaminase 2; TSP-1: thrombospondin-1; u-PA: urokinase-type plasminogen activator; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; YKL-40: chitinase-3-like protein 1*

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| Coagulation cascade pathways | Markers in CU skin | Upregulation | Downregulation | Normal regulation | L/NL skin | Type of CU | TOTAL |
|---|---|---|---|---|---|---|---|
| **Coagulation** | TF | Cugno et al (9)<br>Asero et al (7)<br>Cugno et al (8) | | | L<br>L<br>L | CAU<br>CSU<br>CSU | 3 |
| **Complement** | C5a | Werfel et al (75) | | | L | CSU | 1 |
| **BP involvement** | P selectin | Miyazaki et al (26)<br>Haas et al (19)<br>Zuberbier et al (18) | | | L<br>L<br>L and NL | NS<br>ChU, CoU<br>SD, CSU | 3 |
| | **GRAND TOTAL** | **7** | **0** | **0** | **NA** | **NA** | **7** |
| **Coagula=tion cascade pathways** | **Markers in CU serum** | **Upregulation** | **Downregulation** | **Normal regulation** | **L/NL skin** | **Type of CU** | **TOTAL** |
| **Fibrinolysis/ anti-coagulation** | D-dimers | Grzanka et al (67)<br>Isikcacan et al (64)<br>Cugno et al (9)<br>Zhu et al (6)<br>Chauhan et al (66)<br>Asero et al (7)<br>Asero et al (61)<br>Criado et al (68) | | | NA | CSU<br>CU ns<br>CAU<br>CSU<br>CSU<br>CSU<br>CSU<br>CU ns | 14 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Triwongwaranat et al (69)‡<br>Takeda et al (32)<br>Asero (70)§<br>Wang et al (65)<br>Asero et al (62) | | | | CSU<br>CSU<br>CU ns<br>CU ns<br>CSU | |
| | | | | Takahagi et al (71)† | NA | CSU | |
| | Plasminogen | | | Bork et al (33) | NA | CU ns | 1 |
| | t-PA | | Zhu et al (6) | | NA | CSU | 1 |
| | u-PA antigen<br>suPAR antigen<br>PAI-1 activity | | | Kasperska-zajac et (59) | NA | CSU | 1 |
| | SFMC | Takeda et al (32) | | | NA | CSU | 1 |
| | TT | Chauhan et al (66) | | | NA | CSU | 1 |
| | FDP | Takeda et al (32) | | | NA | CSU | 2 |
| | | | | Takahagi et al (72)† | NA | CSU | |
| | HMWK | Bork et al (33)<br>Zhu et al (6) | | | NA | CU ns<br>CSU | 2 |
| | AT III | | | Bork et al (33) | NA | CU ns | 1 |
| | TM | | Zhu et al (6) | | NA | CSU | 1 |
| | TFPI/Xa | Zhu et al (6) | | | NA | CSU | 1 |
| | **Total** | **19** | **2** | **5** | **NA** | **NA** | **26** |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Coagulation** | TF | | Zhu et al (6) | | NA | CSU | 1 |
| | F1+2 | Cugno et al (9)<br>Zhu et al (6)<br>Asero et al (7)<br>Asero et al (61)<br>Asero et al (62)<br>Asero et al (60)<br>Tedeschi et al (52)¶<br>Xiaoming et al (63) | | | NA | CAU<br>CSU<br>CSU<br>CSU<br>CSU<br>CSU<br>CSU<br>CSU | 9 |
| | | | | Takeda et al (32) | NA | | |
| | Fibrinogen | Takeda et al (32) | | | NA | CSU | 2 |
| | | | | Isikcacan et al (64) | NA | CU ns | |
| | APTT | Chauhan et al (66) | | | NA | CSU | 5 |
| | | | | Isikcacan et al (64)<br>Takeda et al (32)<br>Wang et al (65)<br>Bork et al (33) | NA | CU ns<br>CSU<br>CU ns<br>CU ns | |
| | PT | Chauhan et al (66) | | | NA | CSU | 3 |
| | | | | Isikcacan et al (64)<br>Wang et al (65) | NA | CU ns<br>CU ns | |
| | TAT | Wang et al (65) | | | NA | CU ns | 2 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Zhu et al (6) | | | | CSU | |
| | FIX | | Zhu et al (6) | | NA | CSU | 2 |
| | | | | Bork et al (33) | NA | CU ns | |
| | FX | | | Bork et al (33)<br>Takeda et al (32) | NA | CU ns<br>CSU | 2 |
| | FXII | Bork et al (33) | | | NA | CSU ns | 3 |
| | | | | Takeda et al (32)<br>Asero et al (7) | NA | CSU<br>CSU | |
| | prekallikreine | | | Bork et al (33) | NA | CU ns | 1 |
| | FXI | Bork et al (33) | | | NA | CU ns | 1 |
| | FVIII | Bork et al (33) | | | NA | CU ns | 2 |
| | | | | Takeda et al (32) | NA | CSU | |
| | VWF:Ag | | | Takeda et al (32) | NA | CSU | 1 |
| | FVIIa | Asero et al (7)<br>Wang et al (65)<br>Bork et al (33) | | | NA | CSU<br>CU ns<br>CU ns | 5 |
| | | | | Takeda et al (32)<br>Zhu et al (6) | NA | CSU<br>CSU | |
| | FV | Bork et al (33) | | | NA | CU ns | 1 |
| | FI | | | Bork et al (33) | NA | CU ns | 1 |
| | FII | | | Bork et al (33) | NA | CU ns | 1 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | α2- APL | | | Bork et al (33) | NA | CU ns | 1 |
| | **GRAND TOTAL** | **20** | **2** | **21** | **NA** | **NA** | **43** |
| **BP involvement** | MPV | Chandrashekar et al (24) | | | NA | CSU | **5** |
| | | | Isikcacan et al (64)<br>Akelma et al (74) | | NA | CU ns<br>CSU | |
| | | | | Vezir et al (72)<br>Kasperska-zajac et (73) | NA | CU ns<br>CU ns | |
| | PDW | Chandrashekar et al (24) | | | NA | CSU | **3** |
| | | | | Isikcacan et al (64)<br>Kasperska-zajac et (73) | NA<br>NA | CU ns<br>CU ns | |
| | Nb of BP | Akelma et al (74) | | | NA | CSU | **5** |
| | | | Chandrashekar et al (24)<br>Rajappa et al (43) | | NA | CSU<br>CSU | |
| | | | | Isikcacan et al (64)<br>Kasperska-zajac et (73) | NA | CU ns<br>CU ns | |
| | P2Y12 | Palikhe et al (25) | | | NA | AICU - ATCU | **1** |
| | P-selectin | Chandrashekar et al (24)<br>Zuberbier et al (18) | | | NA | CSU<br>SD and CSU | **4** |
| | | | | Caproni et al (16)<br>Palikhe et al (25) | NA | CSU<br>AICU - ATCU | |
| | **GRAND TOTAL** | **6** | **4** | **8** | **NA** | **NA** | **18** |
| **Complement** | C1 esterase inhibitor | | | Bork et al (33) | NA | CU ns | 1 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | C3 | | | Zhu et al (6) | NA | CSU | 1 |
| | C4 | Zhu et al (6) | | | NA | CSU | 2 |
| | | | | Bork et al (33) | NA | CU ns | |
| | C5a | Zhu et al (6) | | | NA | CSU | 2 |
| | | | | Metz et al (57) | NA | CSU | |
| | **GRAND TOTAL** | **2** | **0** | **4** | **NA** | **NA** | **6** |

*Table legend: data are given as the number of selected articles describing upregulation, downregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) of markers of the coagulation cascade and complement system in CU.* [†]*no significant difference between CU and other types of urticaria;* [‡]*no HC group, elevated DD-dimers in 48% of CSU patients;* [§]*no HC group, elevated DD-dimers in 33% of CSU patients;* [¶]*not specified if statistically significant increase and no data given to extract a clear conclusion. Abbreviations used in table: aPTT: activated partial thromboplastin time; AICU: aspirin-intolerant chronic urticaria; ATCU: aspirin-tolerant chronic urticaria; AT III: antithrombin; α2- APL: α2-antiplasmin; BP: blood platelet; CAU; chronic autoimmune urticaria; CU: chronic urticaria; CU ns: chronic urticaria not further specified; C1 est inh: C1 esterase inhibitor; C4: complement C4; C3: complement C3; C5a: complement C5a; F1+2: prothrombin fragment 1+2; FI: factor I; FII: factor II; FV: Factor V; FVIII: factor VIII; FIX: factor IX; FX: factor X; FXI: factor XI; FXII: factor XII; FVIIa: activated factor VII; FDP: fibrin degradation products; HMWK: high molecular weight kininogen; L: lesional; MPV: mean platelet volume; NA: not applicable; Nb: number;* NL: non-lesional; *PAI-1: plasminogen activator inhibitor-1; PDW: platelet distribution width; Pre-kallikreine; PT: prothrombin time; P2Y12: adenosine diphosphate chemoreceptor; SD: symptomatic dermografism; SFMC: soluble fibrin monomer complex; suPAR: soluble receptor of urokinase-type plasminogen activator; TAT: thrombin-antithrombin complex; TF: Tissue factor; TFPI/Xa: tissue factor pathway inhibitor/activated factor Xa; TM: thrombomodulin; t-PA: tissue-type plasminogen activator; TT: thrombin time; u-PA: urokinase-type plasminogen activator; vWF: von Willebrand Factor; vWF:Ag: von Willebrand Factor antigen*

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| Markers in CU skin | Upregulation | Normal regulation | L/NL skin | Type of CU | TOTAL |
|---|---|---|---|---|---|
| IFN-ɣ | Caproni et al (14)<br>Caproni et al (15) | | L and NL<br>L and NL | CSU<br>CSU | **2** |
| IL-4 | Caproni et al (14)<br>Caproni et al (15)<br>Kay et al (76) | | L and NL<br>L and NL<br>L | CSU<br>CSU<br>CSU | **3** |
| TNF-α | Hermes et al (5) | | L and NL | AU/CSU/DPU | **1** |
| IL-3 | Hermes et al (5) | | L and NL | CoU | **1** |
| IL-33 | Kay et al (76) | | L | CSU | **1** |
| **GRAND TOTAL** | **8** | **0** | **NA** | **NA** | **8** |
| **Markers in CU serum** | **Upregulation** | **Normal regulation** | **L/NL skin** | **Type of CU** | **TOTAL** |
| IL-4 | Hong et al (50) | | NA | CSU | **2** |
| | | Caproni et al (17) | NA | CSU | |
| IL-6 | Hong et al (50)<br>Kasperska-zajac et al (77)<br>Alasandagutti et al (78)<br>Kasperska-zajac et al (79)<br>Grzanka et al (67)<br>Rajappa et al (43)<br>Trinh et al (34) | | NA | CSU<br>CSU<br>CSU<br>CU ns<br>CSU<br>CSU<br>CSU | **8** |
| | | Metz et al (57) | NA | CSU | |
| IL-18 | Kurt et al (81) | | NA | CSU | **4** |

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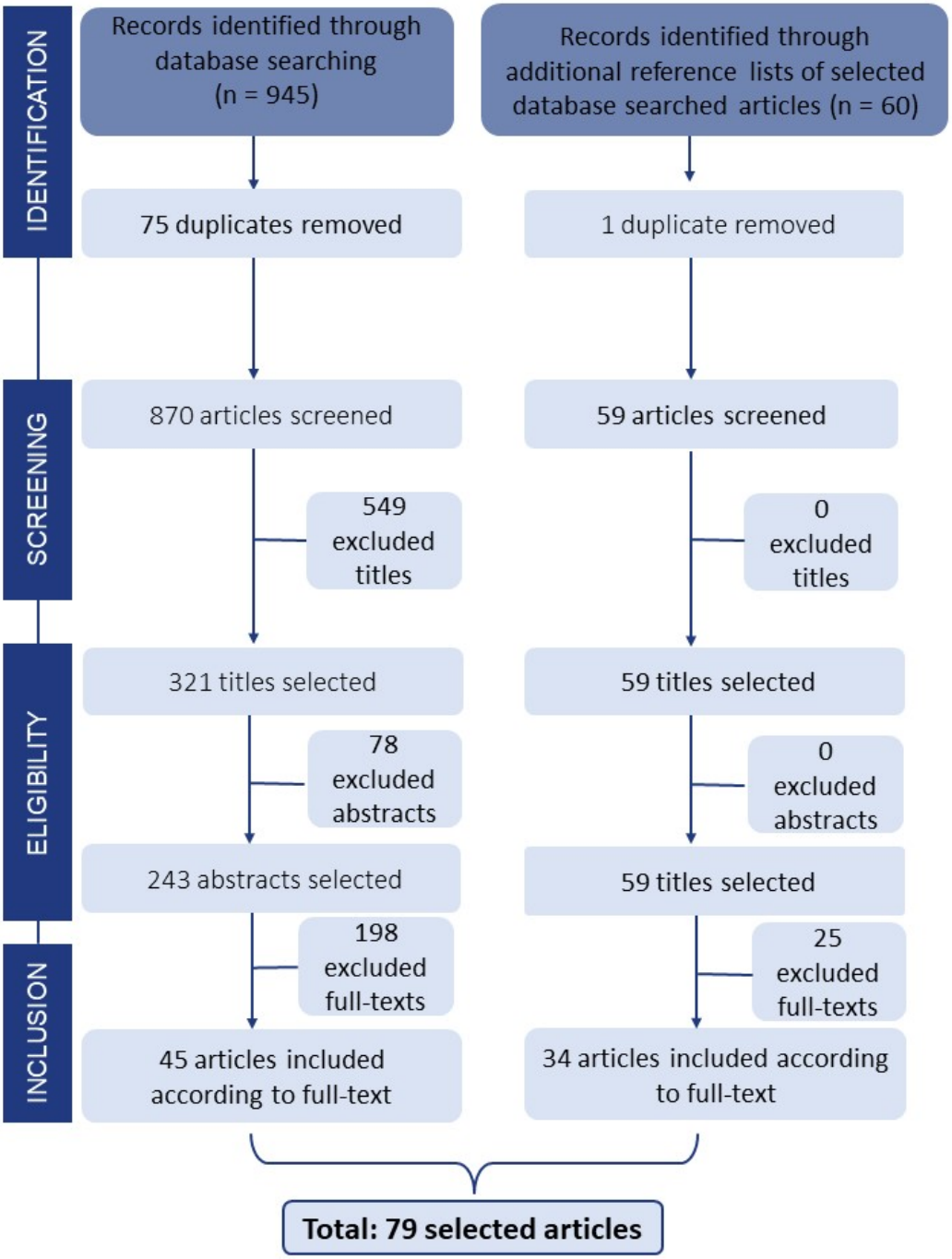
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| | | | | | |
|---|---|---|---|---|---|
| | Puxeddu et al (82) | | | CSU | |
| | | Metz et al (57)<br>Tedeschi et al (80) | NA | CSU<br>CSU | |
| IL-33 | | Metz et al (57)<br>Puxeddu et al (82) | NA | CSU<br>CSU | **2** |
| TNF-α | Hong et al (50)<br>Trinh et al (34) | | NA | CSU<br>CSU | **4** |
| | | Metz et al (57)<br>Tedeschi et al (83) | NA | CSU<br>CSU | |
| IFN-ɣ | Alasandagutti et al (78) | | NA | CSU | **2** |
| | | Caproni et al (17) | | CSU | |
| CCL-5 | Puxeddu et al (22) | | NA | CSU | **1** |
| Hsp-70 | Kasperska-zajac (84) | | NA | CSU | **1** |
| **GRAND TOTAL** | **15** | **9** | **NA** | **NA** | **24** |

*Table legend: data are given as the number of selected clinical articles describing upregulation or normal regulation (i.e. no significant difference in regulation between controls and CU population) in CU or certain CU subtypes, of markers of EC-immune system communication. There was no described downregulation of markers in any of the selected articles. Basic science articles investigating the process of this interaction in vitro are not included in this table. Abbreviations used in table: AU: acute urticaria; CSU: chronic spontaneous urticaria; CU ns: chronic urticaria not specified; DPU: delayed pressure urticaria; IL-: interleukin-; CCL-5: chemokine ligand 5;* CU: chronic urticaria; hsp-70: heat shock protein 70; *IFN-ɣ: interferon gamma; L: lesional; NL: non-lesional; TNF-α: tumor necrosis factor alpha*

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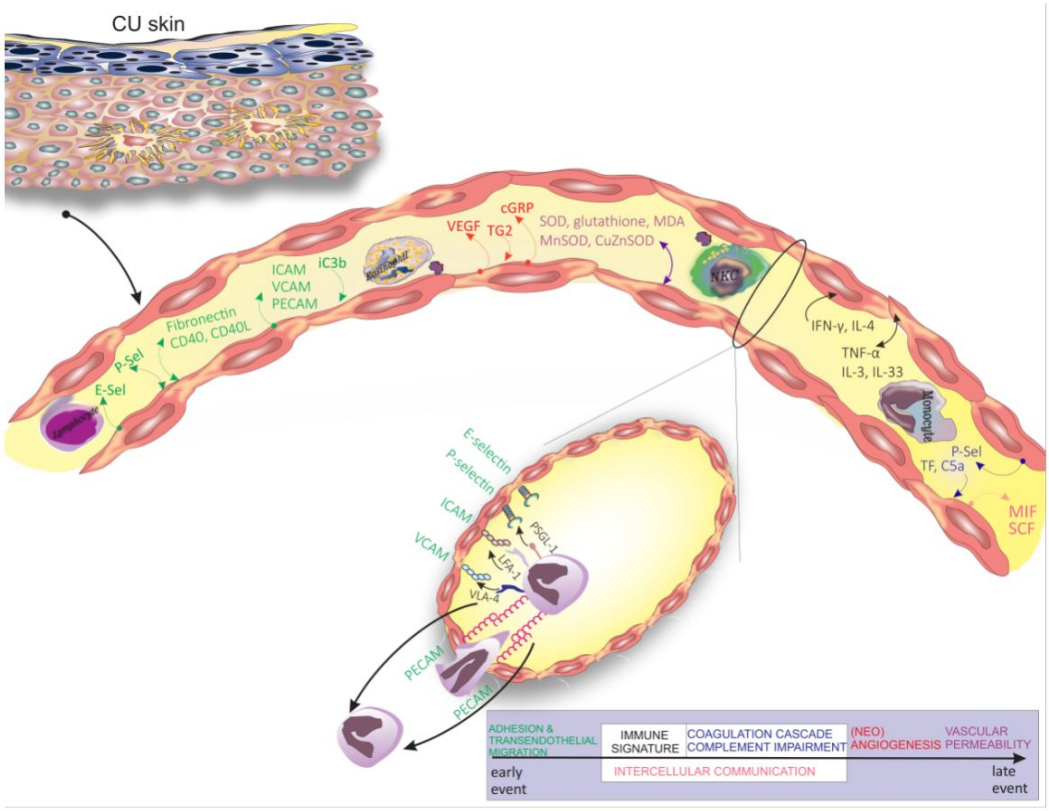
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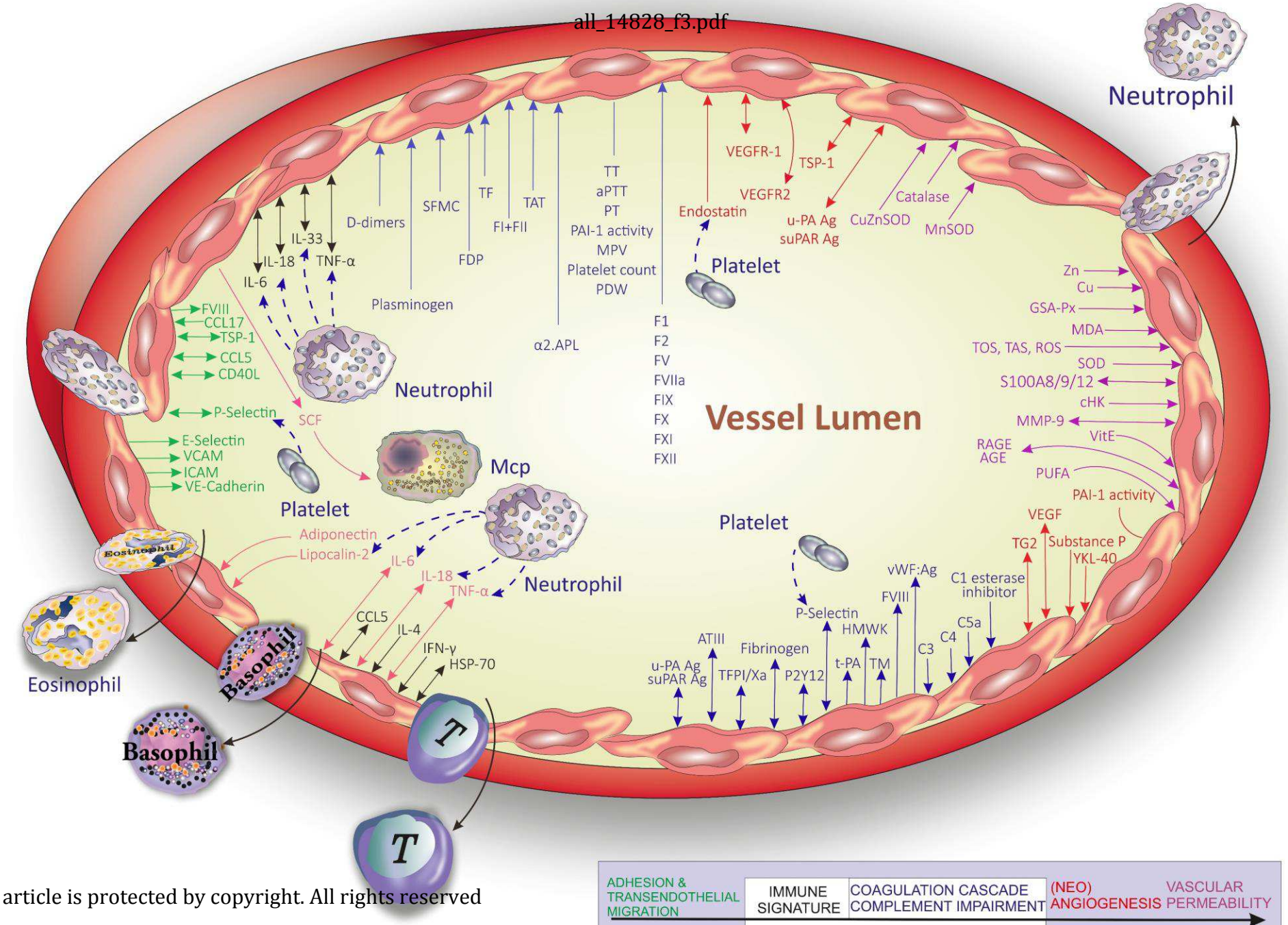



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**Supplementary file I: Details on search strategy using the Prisma 2009 checklist (14)**

1) Description of information sources
   1.1 **Pubmed:** first search done on the 30th of October 2018, last update performed on the first of April 2020.
   1.2 **The Cochrane Library**: first search done on the 30th of October 2018, last update performed on the first of April 2020.
   1.3 **Web of Science**: first search done on the 30th of October 2018, last update performed on the first of April 2020.
   1.4 **SCOPUS**: first search done on the 30th of October 2018, last update performed on the first of April 2020.

2) Full electronic search strategy
   **On Pubmed/The Cochrane Library/Web of Science/SCOPUS**: a combination of the following Mesh terms was used:
   chronic urticaria AND pathogenesis AND (vasculopathy OR microangiopathy OR endothelial cells OR marker)

   No limitation on publication date was added.
   Language limitations (English, French, Dutch, German) were added during selection based on title of article.
   Duplicates were manually removed when articles of all databases were put together to form a list.
   Titles without abstract or full text were excluded.
   All study designs with the exception of reviews, editorials and case studies were included

3) Results with reasons for full text exclusions
   *For the originally selected articles*: n = 198
   3.1. Not about the topic: n = 82
   - Another disease (other than chronic urticaria): n = 14
   - Not about the role of ECs in chronic urticaria or about the role of cells other than ECs in chronic urticaria n = 68
   3.2. Reviews/editorial/case reports: n = 82
   3.3. Language: n = 9
   3.3. No full text available: n = 25

   *For the additional references*: n = 25
   3.1. Not about the topic: n = 20
   - Another disease (other than chronic urticaria): n = 4
   - Not about the role of ECs in chronic urticaria or about the role of cells other than ECs in chronic urticaria n = 16
   3.2. Reviews/editorial/case reports: n = 5
   3.3. Language: n = 0
   3.3. No full text available: n = 0

**Supplementary file II. Quality assessment (QA) of the selected articles using the QA tool for observational studies adapted from the national institute of health (13)**

Question 1 (Q1): Was the research question or objective in this paper clearly stated?

Question 2 (Q2): Was the study population clearly specified and defined?

Question 3 (Q3): Was the participation rate of eligible persons at least 50%?

Question 4 (Q4): Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

Question 5 (Q5): Was a sample size justification, power description, or variance and effect estimates provided?

Question 6 (Q6): For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

Question 8 (Q8): For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

Question 7 (Q7): Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

Question 9 (Q9): Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Question 10 (Q10): Was the exposure(s) assessed more than once over time?

Question 11 (Q11): Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Question 12 (Q12): Were the outcome assessors blinded to the exposure status of participants?

Question 13 (Q13): Was loss to follow-up after baseline 20% or less?

Question 14 (Q14): Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)

Question 15 (Q15): How do reviewers rate the overall quality?

| AUTHORS | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | REASON | YEAR OF PUBLICATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hofman et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2020 |
| Chauhan et al | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | NR | NR | Y | F | | 2019 |
| Zhou et al [1] | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2019 |
| Zhou et al [2] | Y | N | NR | NR | N | Y | NR | N | N | N | Y | NR | NR | Y | P | Letter to the editor | 2019 |
| Zhang et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2019 |
| Grzanka et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2018 |
| Kasperska-Zajac et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2018 |
| Vezir et al | Y | N | NR | NR | N | NR | CD | N | N | N | Y | NR | NR | Y | P | Population, exposure and outcome measures poorly defined | 2018 |
| Chen et al | Y | N† | NR | Y | N | Y | Y | Y | Y | NR | Y | NR | NR | Y | G | | 2017 |
| Trinh et al | Y | N | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2016 |
| Hong et al | Y | N | NR | NR | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2016 |
| Dilek et al | Y | Y | NR | Y | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2016 |
| Kasperska-Zajac et al | Y | N | NR | Y | N | N | NA | Y | Y | Y | Y | NR | NR | Y | F | | 2016 |
| Dilek et al | Y | Y | NR | Y | N | N | NA | Y | Y | N | Y | NR | NR | Y | G | | 2016 |
| Kasperska-Zajac et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2015 |
| Kay et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2015 |
| Isiksacan et al | Y | N | NR | NR | N | Y | NR | N | Y | N | Y | NR | NR | Y | F | | 2015 |
| Akelma et al | Y | Y | NR | Y | N | Y | Y | N | Y | N | Y | NR | NR | Y | F | | 2015 |
| Cugno et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2015 |
| Jagodzinska et al | Y | N | NR | NR | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2015 |
| Alasandagutti et al | Y | N† | NR | Y | N | Y | Y | N | Y | N | Y | NR | NR | Y | F | | 2014 |
| Grzanka et al | Y | N | NR | Y | N | N | NA | Y | Y | Y | Y | NR | NR | Y | F | | 2014 |
| Palikhe et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2014 |
| Kay et al | Y | N† | NR | NR | N | N | NA | N | Y | N | Y | NR | NR | Y | F | | 2014 |
| Metz et al | Y | N† | NR | NR | N | N | NA | Y | Y | N | Y | NR | NR | NR | P | Letter to the editor | 2014 |
| Chandrashekar et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | Y | NR | Y | F | | 2014 |
| **AUTHORS** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** | **Q12** | **Q13** | **Q14** | **Q15** | **REASON** | **YEAR OF PUBLICATION** |
| Kasperska-zajac et al | Y | N | NR | Y | N | Y | Y | Y | N | N | Y | NR | NR | Y | F | | 2014 |
| Puxeddu et al | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | NR | NR | Y | F | | 2014 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kay et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2014 |
| Puxeddu et al[3] | Y | N | NR | NR | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Metz et al | Y | N† | NR | N | N | Y | NR | Y | Y | N | NR | NR | NR | Y | P | Letter to the editor | 2013 |
| Zhu et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2013 |
| Rajappa et | Y | N† | NR | NR | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Criado et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Triwongwaranat et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Asero et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Puxeddu et al[4] | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2013 |
| Jasinka et al | Y | N | NR | NR | N | NR | NR | Y | Y | N | Y | NR | NR | Y | F | | 2012 |
| Sagdic et al | Y | N† | NR | NR | N | N | NA | N | Y | N | Y | NR | NR | Y | F | | 2011 |
| Kasperska-zajac et al | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | NR | NR | Y | F | | 2011 |
| Takeda et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2011 |
| Asero et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2011 |
| Kurt et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2011 |
| Takahagi et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2010 |
| Tedeschi et al | Y | N† | NR | Y | N | N | NA | Y | Y | Y | Y | NR | NR | Y | F | | 2010 |
| Tedeschi et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2009 |
| Cugno et al | Y | N† | NR | Y | N | Y | Y | N | Y | N | Y | NR | NR | Y | F | | 2009 |
| Wang et al | Y | N | NR | NR | N | NR | NR | N | N | N | Y | NR | NR | Y | P | Correspondence | 2009 |
| Altrichter et al | Y | N | NR | Y | N | Y | Y | Y | Y | Y | Y | NR | NR | Y | G | | 2009 |
| Asero et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2008 |
| Tedeschi et al | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2007 |
| Asero et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2007 |
| Kasperska-zajac et al[5] | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2007 |
| Kasperska-zajac et al[6] | Y | N | NR | NR | Y | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2007 |
| Xiaoming et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2007 |
| Miyazaki et al | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | In vitro study | 2006 |
| Szegedi | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2006 |
| Asero et al | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2006 |
| **AUTHORS** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** | **Q12** | **Q13** | **Q14** | **Q15** | **REASON** | **YEAR OF PUBLICATION** |
| Cassano et al | Y | N | NR | NR | N | Y | Y | Y | Y | Y | Y | NR | NR | Y | G | | 2006 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Caproni et al[7] | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | NR | NR | Y | F | | 2006 |
| Caproni et al[8] | Y | N† | NR | Y | N | Y | Y | Y | Y | N | Y | NR | NR | Y | G | | 2006 |
| Tedeschi et al | Y | N | NR | NR | N | Y | Y | N | Y | N | Y | NR | NR | Y | P | Population and outcome measure was poorly described | 2006 |
| Tedeschi et al | Y | Y | NR | Y | N | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2005 |
| Kessel et al | Y | N | NR | Y | Y | N | NA | Y | Y | N | Y | NR | NR | Y | F | | 2005 |
| Caproni et al | Y | N | NR | NR | N | Y | Y | Y | Y | N | Y | NR | NR | Y | F | | 2005 |
| Caproni et al | Y | N | NR | NR | N | N | NA | N | N | N | Y | NR | NR | Y | P | No description of exposure, population poorly described | 2003 |
| Raho et al | Y | N | NR | NR | N | N | NA | N | Y | N | Y | NR | NR | Y | F | | 2003 |
| Asero et al | Y | Y | Y | Y | N | N | NA | N | Y | N | Y | NR | NR | N | F | | 2003 |
| Lee et al | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | In vitro study | 2002 |
| Briganti et al | Y | N | NR | Y | N | Y | Y | Y | Y | Y | Y | NR | NR | N | F | | 2001 |
| Hermes et al | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | Y | NR | Y | G | | 1999 |
| Haas et al | Y | N | NR | NR | N | Y | NR | Y | Y | N | Y | NR | NR | NA | P | Population not described, few patients (only 4) | 1998 |
| Hermes et al | Y | N | NR | NR | N | Y | NR | N | N | NR | Y | NR | NR | Y | P | Population not described, few patients (only 8) | 1997 |
| Werfel et al | Y | N | NR | NR | N | NR | NR | N | N | N | Y | NR | NR | N | P | No statistics, no description of exposure | 1997 |
| Zuberbier et al | Y | N | NR | NR | N | N | NA | N | Y | N | Y | NR | NR | Y | F | | 1997 |
| Haas et al | Y | N | NR | NR | N | Y | NR | N | N | Y | Y | NR | NR | N | P | Population not described, few patients (only 7) | 1995 |
| Barlow et al | Y | N | NR | NR | N | Y | NR | N | Y | Y | Y | NR | NR | Y | F | | 1994 |
| Czarnetzki et al | Y | N† | NR | Y | N | N | NA | Y | Y | N | Y | NR | NR | N | F | | 1989 |
| Bork et al | Y | N | NR | NR | N | NR | NR | N | N | N | Y | NR | NR | N | P | No description of exposure, population poorly described (few patients, only 10), statistics difficult to interprete | 1984 |

†Description of population in place but not in time

[1] Indian J of Dermatol

[2] Ann Allergy Asthma Immunol

[3] Int Arch Allergy Immunol
[4] Cytokine
[5] Kasperska-Zajac A, Brzoza Z, Rogala B. Blood urokinase plasminogen activator system in chronic urticaria. Arch Dermatol Res. 2007;298(8):409-11.
[6] Kasperska-Zajac A, Brzoza Z, Polaniak R, Rogala B, Birkner E. Markers of antioxidant defence system and lipid peroxidation in peripheral blood of female patients with chronic idiopathic urticaria. Arch Dermatol Res. 2007;298(10):499-503
[7] Int J Immunopathol Pharmacol.
[8] Br J Dermatol.

Abbreviations used in table: N: no; Y: yes; CD: cannot determine; F: fair; G: good; NA: not applicable; NR: not reported; P: poor

**Supplementary file III. Summary of all 79 selected articles**

| Nb | Authors | Biomarker(s) | Summary of results |
|---|---|---|---|
| 1 | Hofman et al (2020) | cHK | cHK was elevated in CSU patients compared to healthy controls. cHK levels normalized in patients that were in disease remission. Moreover, the observed increases in cHK levels were comparable to previously determined levels in HAE-1 and HAE-2. Increased cHK was not limited to CSU patients with angioedema and not associated with antihistamine responsiveness. |
| 2 | Chauhan et al (2019) | D-dimers<br>TT<br>PT<br>aPTT | Plasma D-dimer in 23% patients and 4% controls and PT and aPTT in 63% and 5% patients, respectively, were significantly higher compared with 58% and 1% of controls, respectively. About 18 of 72 (25%) patients with high UAS of ≥16-42 were compared with 5 of 28 (17.8%) patients with UAS7 of ≤15. Patients with elevated plasma D-dimer levels had significantly more systemic symptoms (86.9%) compared with patients with normal plasma D-dimer levels (81.8%). |
| 3 | Zhou et al (2019)[1] | S100A8<br>S100A9<br>S100A12 | The plasma levels of S100A8, S100A9 and S100A12 were significantly higher in CSU patients than those in controls. Interestingly, the level of S100A12 significantly correlated with S100A8 and S100A9 in CSU patients ($p < 0.05$ and $p < 0.001$, respectively). In addition, S100A8, S100A9 and S100A12 all significantly inversely correlated with blood basophil percentage. |
| 4 | Zhou et al (2019)[2] | YKL-40 | Patients with CSU had significantly higher YKL-40 serum levels than healthy controls ($p = 0,0121$). |
| 5 | Zhang et al (2019) | CCL17 | Upregulated or downregulated miRNAs were validated by reverse transcription qPCR in sera from 59 active CSU patients and 58 healthy controls. The expression of miR-125a-5p was significantly upregulated in CSU sera and serum levels of CCL17 were also significantly increased in CSU patients. Serum miR-125a-5p expressions were found to be further upregulated in refractory CSU cases (n = 10). In 12 CSU patients in remission, serum miR-125a-5p expression and miR-125a levels were significantly decreased as compared with that obtained in active phase patients. |
| 6 | Vezir et al (2018) | MPV | There was no significant difference in median MPV levels of patients with chronic urticaria and the control group ($p > 0,05$). |
| 7 | Grzanka et al (2018) | IL-6<br>D-dimers<br>CRP | Serum concentrations of IL-6, CRP and D-dimer were significantly higher in CSU patients as compared with controls. Also, statistically significant correlations between D-dimers concentrations and the inflammatory markers (CRP and IL-6) as well as UAS were found. |
| 8 | Kasperska-Zajac et al (2018) | Hsp-70 | Plasma Hsp-70 concentrations were significantly higher in CSU (all) and mild CSU patients as compared with the controls. Moderate-severe CSU patients tended to show higher Hsp-70 concentration as compared with the controls, but not with mild activity of the disease. There were no significant differences in Hsp-70 concentration between moderate-severe and mild CSU patients. Serum anti-Hsp-70 antibodies concentrations were significantly higher in CSU (all) and mild CSU in comparison to the controls. Association was observed between anti-Hsp-70 antibodies and increased CRP concentration; however, no correlation between anti-Hsp-70 and Hsp-70 concentrations was seen in the patients. |

**Supplementary file III. Summary of all 79 selected articles**

| | | | |
|---|---|---|---|
| 9 | Chen et al (2017) | sVE-cadherin | Serum levels of sVE-cadherin in patients with CSU were significantly higher than those in patients with atopic dermatitis and healthy controls. Serum sVE-cadherin levels in patients with CSU were correlated with the severity of CSU according to UAS. In addition, histamine markedly induced sVE-cadherin release in HDMEC-1 cells. |
| 10 | Trinh et al (2016) | adiponectin<br>leptin<br>LCN2<br>IL-10<br>IL-6<br>TNF-α | Mean levels of serum LCN2, TNF-α, IL-6, and IL-10 were significantly higher in CU patients than in controls. Adiponectin levels were significantly lower in patients with CU than in controls. While serum IL-6 levels were significantly higher in refractory CU patients, compared to responsive CU individuals, LCN2 levels were significantly lower. LCN2 inhibited fMLP-induced neutrophil migration. LCN2 showed a direct relationship with UAS ($\beta = -0.274$, $p < 0.001$). |
| 11 | Hong et al (2016) | TG2<br>c-kit receptor | TG2 activity was significantly higher in serum samples from patients with CSU than in serum samples from healthy controls ($p < .001$). Colocalization of mast cell surface marker c-kit and TG2 was significantly increased in the lesional skin of patients with CSU compared with that in healthy controls. The levels of histamine, leukotriene C4, TNF-α, TGF-β, and IL- 4/5/6 were significantly higher in patients with CSU than in healthy controls ($p < .001$). Serum TG2 levels had positive correlations with each inflammatory mediator ($p < .001$). TG2 activity was increased in cord blood-derived human mast cells (CBMCs) and peripheral blood-derived human mast cells activated with IgE compared with those without activation ($p < .05$). |
| 12 | Dilek et al (2016) | ROS | Plasma oxidative stress is increased in children with CSU when compared to healthy subjects, and plasma oxidative stress markers positively correlate with disease activity. |
| 13 | Kasperska-Zajac et al (2015) | sRAGE | Serum sRAGE concentrations were significantly decreased in CSU patients, especially those more severely affected. |
| 14 | Dilek et al (2015) | MMP-9 | There was a statistically significant difference in plasma MMP-9 median value between CSU patients and healthy controls ($p < 0.001$). Also, MMP-9 levels showed a significant positive correlation with UAS (rho = 0.57, $p < 0.001$). Twenty-six percent of patients had ASST results. Neither UAS nor plasma MMP-9 levels were significantly different between ASST-positive and -negative patients ($p > 0.05$). |
| 15 | Kasperska-Zajac et al (2015) | IL-6<br>sIL-6<br>sgp130 | Concentrations of IL-6, IL-6 sR, sgp130 in plasma were significantly elevated in CSU patients compared with healthy controls. IL-6 correlated significantly with sgp130. By contrast, IL-6 did not correlate significantly with IL-6 sR. However, significant correlation was noted between IL-6 sR and sgp130. |
| 16 | Kay et al (2015) | IL-4<br>IL-5<br>IL-25 | There were increases in IL-4(+) and IL-5(+) cells in lesional skin vs. controls ($p = 0{\cdot}03$ and $p < 0{\cdot}001$, respectively) and marked elevations in the numbers of IL-33(+), IL-25(+) and TSLP(+) cells in the dermis of L skin vs. both NL skin ($p = 0{\cdot}002$, $p = 0{\cdot}01$ and $p = 0{\cdot}04$, respectively) and controls ($p = 0{\cdot}001$, $p < 0{\cdot}001$ and $p = 0{\cdot}005$, respectively). There was also a correlation between the numbers of IL-33(+) and IL-25(+) cells |

**Supplementary file III. Summary of all 79 selected articles**

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| | | IL-33<br>TSLP | (r = 0·808, p = 0·015). IL-33 localized to CD31(+) ECs, CD90(+) fibroblasts, CD68(+) macrophages and tryptase(+) mast cells, whereas IL-25 was expressed by epithelial cells, mast cells and major basic protein-positive eosinophils. IL-33 and IL-25 were constitutively expressed in the epidermis of both controls and patients with CSU. |
| 17 | Isiksacan et al (2015) | D-dimers<br>fibrinogen<br>aPTT<br>PT<br>ristocetin<br>ADP<br>TRAP<br>MPV<br>PDW<br>number of blood platelets | In patients with CU, significantly decreased platelet aggregation to some agonists (ristocetin and TRAP) was observed. The D-dimer levels were elevated, mean platelet volume was decreased, but no alteration was observed in other coagulation assays. Elevated D-dimer levels indicated that coagulation and fibrinolysis are activated in the patients with CU. |
| 18 | Akelma et al (2015) | MPV | MPV (fL) levels were significantly lower in children with CU when compared to healthy children (7.42 ± 0.77 and 7.89 ± 0.65, respectively; p = 0.004). Mean platelet number was significantly higher in children with CU when compared to healthy children (p = 0.008, p = 0.014, respectively). |
| 19 | Cugno et al (2015) | F1+2<br>D-dimer<br>TF | F1+2 and D-dimer levels were higher in active chronic autoimmune urticaria (276.5±89.8 pmol/L and 5.56±4.40 nmol/L, respectively) than in controls (145.2±38.0 pmol/L and 1.06±0.25 nmol/L; p = 0.029 and p = 0.011). Tissue factor positivity was evident in skin biopsies of autoimmune chronic urticaria. F1+2 and D-dimer, during remission, were markedly reduced in autoimmune chronic urticaria. |
| 20 | Jagodzinska et al (2015) | VEGF<br>sVEGFR1<br>sVEGFR2 | There were no significant differences in VEGF concentration between CSU groups and healthy subjects. Contrary, VEGF concentration was significantly higher in DPU and CSU/Hashimoto patients as compared with the healthy subjects and CSU groups. Furthermore, VEGF value in CSU/Hashimoto patients during the remission was similar to that of the active period and significantly higher than the healthy subjects; VEGF concentration was significantly correlated with TSH. Plasma concentrations of sVEGF1 and sVEGF2 were similar in chronic urticaria patients and the healthy subjects. |
| 21 | Alasandagutti et al (2014) | IFN-γ<br>IL-6 | A significant (p < 0.0001) increase in serum cytokine levels of IFN-γ and IL-6 was recorded in chronic idiopathic urticaria patients compared to healthy controls |

**Supplementary file III. Summary of all 79 selected articles**

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| 22 | Grzanka et al (2014) | AGEs | Serum AGEs and albumin concentrations in CSU patients were significantly lower as compared with the healthy subjects. Significant positive correlation was observed between AGEs and albumin concentrations in the subjects. |
| 23 | Palikhe et al (2014) | P2Y12 receptor<br>P-selectin<br>soluble P-selectin | The expression of P2Y12 was significantly higher in patients with CU compared with controls, whereas no significant difference was noted in the expression of P-selectin level. The levels were not significantly different according to urticaria symptom score, symptom control status, and aspirin intolerance. Soluble P-selectin level was significantly higher in the AICU group than in the ATCU group compared with controls. Aspirin did not significantly suppress P2Y12 and P-selectin expressions on platelets in the AICU group, whereas significant suppression was noted in the ATCU group. |
| 24 | Kay et al (2014) | cGRP and VEGF | Lesional skin in CSU contained significantly more cGRP+ and VEGF+ cells than non-lesional skin. No significant differences were observed in cGRP and VEGF expression between non-lesional skin and controls. In lesional skin, VEGF and cGRP co-localised to UEA-1+ blood vessels. cGRP was also expressed by neutrophils and eosinophils and to a lesser extent by CD90(+) fibroblasts, mast cells, CD3(+) and CD68(+) cells. cGRP and VEGF expression was not related to the duration of disease. |
| 25 | Metz et al (2014) | Substance P | Authors show that substance P is increased in CSU patients and that only disease activity but not underlying cause of disease, occurrence of angioedema, or psychosomatic comorbidities are correlated with serum concentrations of substance P. |
| 26 | Chandrashekar et al (2014) | Substance P<br>MVP<br>PDW | There was a significantly higher MPV and PDW in patients with CU when compared to controls. Platelet aggregation and soluble P-selectin levels were significantly higher in patients with CU, as compared to controls. Urticaria severity score correlated positively with platelet aggregability and soluble P-selectin levels. APST-positive patients had significantly higher platelet aggregation and higher soluble P-selectin levels, when compared to the APST-negative patients, indicating more platelet activation in the autoimmune group. |
| 27 | Xiaoming et al (2014) | F1+2 | The levels of F1+2 in autoimmunity CU patients decreased after treatment (loratadine and dipyridamole). Before treatment, the levels of the treatment group was significantly higher than those of the control group. |
| 28 | Kasperska-zajac et al (2014) | number of platelets<br>MDV<br>PDW | No significant differences were found in MPV and PDW between CSU group and the healthy subjects. The platelet count was significantly higher in moderate-severe CSU than that of the controls and mild CSU patients. Serum CRP concentrations were significantly higher in CSU patients as compared with the healthy subjects and significantly correlated with the platelet count in CSU patients. |
| 29 | Puxeddu et al (2014) | endostatin<br>TSP-1 | The serum levels of the anti-angiogenic mediators endostatin and TSP-1 resulted significantly higher in CSU than in control subjects. |

**Supplementary file III. Summary of all 79 selected articles**

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| 30 | Kay et al (2014) | PECAM (CD31) | Lesional skin in CSU contained significantly more CD31+ ECs, CD31+ blood vessels, neutrophils, eosinophils, basophils, macrophages and CD3+ T cells than non-lesional skin. Increased vascularity was confirmed by confocal imaging using the lectin UEA-1. Uninvolved skin from CSU contained significantly more CD31+ ECs, CD31+ blood vessels and eosinophils compared with the control subjects. There was a threefold increase in mast cell numbers when CSU was compared with controls but no difference was observed between lesional and uninvolved skin. |
| 31 | Puxeddu et al (2013)[3] | CCL5/RANTES | We detected a significantly higher concentration of CCL5/RANTES ($p < 0.0001$) but not of CXCL8/IL-8 in CSU patients compared to healthy control subjects. The serum levels of sICAM-1 and sVCAM-1 were significantly increased in CSU patients compared to NHS ($p = 0.0121$ and $p = 0.0043$, respectively). No difference in chemokine or soluble adhesion molecule levels was detected between the ASST-positive and ASST-negative subgroups. A positive correlation was found between sICAM-1 and sVCAM-1 ($p = 0.0022$) but not between these and CCL5/RANTES. |
| | | CXCL8/IL-8 | |
| | | sVCAM-1 | |
| | | sICAM-1 | |
| 32 | Metz et al (2013) | TNF | There was no significant correlation between any of the biomarkers evaluated and the disease activity. |
| | | C5a | |
| | | IL-6 | |
| | | IL-18 | |
| | | IL-33 | |
| | | TSLP | |
| | | VEGF | |
| 33 | Zhu et al (2013) | D-dimer | Plasma levels of FVIIa were not significantly different in CU patients ($p > 0.05$), while levels of TAT and F1+2 were significantly higher in CU patients ($p < 0.01$) compared to controls. Plasma levels of TFPI/Xa were higher, whereas levels of TM, FIX and TF were lower in CU patients compared to controls ($p < 0.01$). Plasma levels of D-dimer and HMWK in CU patients were increased significantly ($p < 0.01$), while levels of t-PA were decreased ($p < 0.01$) compared to controls. Concentrations of C5a and C4 in CU plasma and serum respectively, were superior to those in healthy controls ($p < 0.01$). |
| | | TAT | |
| | | TM | |
| | | t-PA | |
| | | TFPI/Xa | |
| | | TF | |
| | | F1+2 | |
| | | HWMK | |
| | | FIX | |
| | | FVII | |

**Supplementary file III. Summary of all 79 selected articles**

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| 34 | Rajappa et al (2013) | MDA<br>SOD<br>GSH-Px<br>IL-6 | In patients with CSU, platelet SOD and GSH-Px were significantly lowered, while platelet MDA levels were significantly elevated in comparison to healthy controls. IL-6 was significantly elevated in patients with CSU and correlated with platelet oxidative stress parameters ($p < 0.05$). Platelet MDA, SOD, GSH-Px and inflammatory marker plasma IL-6 showed a significant correlation with USS in patients with CSU. |
| 35 | Criado et al (2013) | D-dimer | Patients with active CU had the highest serum levels of D-dimers ($p < 0.01$), when compared to patients with CU under remission and the control group (patients with psoriasis). |
| 36 | Triwongwaranat et al (2013) | D-dimer | Plasma D-dimer level was abnormal in 48.3% of CSU patients. The study showed statistically significant positive correlation between disease severity and plasma D-dimer level ($p < 0.05$, $r = 0.537$). There was no statistically significant difference in plasma D-dimer level between APST positive and negative groups, and also between ASST positive and negative groups. In APST negative group, plasma D-dimer level was elevated in 29 patients (47.5%) and correlated with disease severity. |
| 37 | Asero (2013) | D-dimer | D-dimer plasma levels were elevated in 30 of 91 (33%) patients. Plasma D-dimer levels were elevated in 0 of 41 (0%) patients showing an “excellent” response to cetirizine, 3 of 14 (21%) patients showing a “good” response, 3 of 5 (60%) patients showing a “partial” response, 18 of 23 (78%) patients showing a “poor” response, and 7 of 8 (88%) non-responders. |
| 38 | Puxeddu et al (2013)[4] | IL-18<br>IL-33 | Total IL-18, IL-18-binding protein and free IL-18 serum levels were significantly higher in CSU than in controls. IL-18 and IL-18-binding protein increased significantly in both ASST-positive and negative subgroups. Free IL-18 resulted significantly higher in the ASST-negative, but not in the ASST-positive subgroup. No differences in IL-33/sST2 levels were detected between CSU and controls. Increased levels of free IL-18 and IL-18-binding protein, but not IL-33, was detected in CSU. |
| 39 | Jasinka et al (2012) | CD-40L | The plasma sCD40L level did not differ significantly between ASST-negative CU patients, ASST-positive CU patients and healthy controls. The plasma sCD40L level did not significantly correlate with the UAS7 in the two CU groups and in patients with CU as a whole. |
| 40 | Sagdic et al (2011) | MDA<br>GSH- Px<br>Zn<br>CuZn-SOD<br>Cu | While erythrocyte MDA levels, erythrocyte GSH- Px activities and erythrocyte Zn levels showed no differences between the patient and control groups, a statistically significant decrease and increase were observed in erythrocyte CuZn-SOD activities and Cu levels, respectively, in the chronic idiopathic urticaria patients when compared to those of the controls ($p < 0.001$ for both of them). |
| 41 | Kasperska-zajac et al (2011) | IL-6 | IL-6 was significantly increased in CU patients as compared with the healthy subjects, whereas it decreased remarkably upon the spontaneous remission. IL-6 concentration was associated with weekly urticaria activity scores and also significant differences were found between patients showing different degrees of urticarial activity. |

**Supplementary file III. Summary of all 79 selected articles**

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| 42 | Takeda et al (2011) | fibrinogen<br>D-dimer<br>fibrin<br>FDP<br>SFMC<br>APTT | Classical coagulation assays revealed that levels of fibrinogen, D-dimer, and fibrin and FDP, and positive rates of SFMC were significantly elevated in patients with CU, whereas the elevation of F1 + 2 was not statistically significant. On the other hand, all parameters of a global coagulation test, APTT clot waveform analysis, evidently showed a hypercoagulable pattern and were significantly correlated to disease severity of CU. |
| 43 | Asero et al (2011) | F1+2<br>D-dimer | F1+2 and D-dimer were elevated in 7/16 APST-negative CU patients. The activation of the coagulation cascade was associated with disease severity. In patients with APST-negative CU, mean F1 + 2 level [242.8 ± 33.7 pmol/L (ESM)] was higher than in normal controls (151.8 ± 9.09 pmol/L; p = 0.002) but lower than in autoreactive patients (526.2 ± 97.8 pmol/L; p = 0.05). Similarly, mean D-dimer level was higher than in normal controls (484.2 ± 148.3 ng/mL vs. 229.5 ± 16.7 ng/mL; p = 0.03) but lower than in autoreactive patients (1142.2 ± 317.4 ng/mL; p = 0.05). |
| 44 | Kurt et al (2011) | IL-18 | Positive response to ASST and serum IL-18 levels were higher in CSU patients than those with respiratory diseases (asthma and SAR) (p = 0.034 and 0.002, respectively) and normal controls (p = 0.004 and 0.031, respectively). Considering all patients, IL-18 levels were higher in patients with positive ASST (301.8 ± 194.4 vs. 241.8 ± 206.3 pg/ml, p = 0.036) than ASST negative patients. |
| 45 | Takahagi et al (2010) | FDP<br>D-dimer | The levels of FDP in patients with CU were significantly higher than those in patients with IU, but no other differences in FDP and D-dimer were observed among patients with different types of urticaria. These markers of patients with CU were well correlated with each other and significantly associated with disease severity of CU, but not with skin reactions to autologous serum. |
| 46 | Tedeschi et al (2010) | MMP-9 | Plasma levels of MMP-9 were significantly higher in CU patients than in healthy controls (p = 0.0001, 0.003 and 0.005, respectively) and a trend towards a higher MMP-9/TIMP-1 molar ratio was found (p = 0.051). A significant correlation was found between plasma MMP-9 levels and urticaria severity score (r=0.48, p < 0.0001). |
| 47 | Tedeschi et al (2009) | VEGF<br>F1+2 | Plasma VEGF concentrations were higher in CU patients (8.00 +/- 0.90 pmol/l) than in controls (0.54 +/- 0.08 pmol/l) (p = 0.0001) and tended to parallel both the severity of CU and to correlate with F1+2 levels. Immunohistochemically, all specimens from patients with CU showed a strong expression of VEGF (p = 0.002) that colocalized with ECP, a classic eosinophil marker. |
| 48 | Cugno et al (2009) | TF | All specimens from patients with CU clearly showed TF expression that was absent in all normal control specimens (p = 0.0001) and in the skin disorders with non-eosinophilic infiltrates (p = 0.001-0.0001). The double-staining experiments for TF and eosinophil cationic protein clearly showed that the TF-positive cells were eosinophils. |
| 49 | Wang et al (2009) | PT | PT and APTT were in the normal range, and the levels of FVIIa, TAT, and D-dimer were all significantly |

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| | | APTT<br>D-dimer<br>TAT<br>FVII | elevated. Although in the cases studied only the level of FVIIa was significantly correlated with the disease activity (r= 0.5110; p <0 .05), the positive correlations were shown between levels of FVIIa and TAT (r = 0.6493; p < .001), and TAT and D-dimer (r = 0.6318; p < .001). |
| 50 | Altrichter et al (2009) | Total MMP-9<br>active MMP-9 | Significantly increased levels of total and active MMP-9 were detected in patients with CU as compared to healthy controls. Interestingly, patients with psoriasis also had clearly elevated plasma levels of total and active MMP-9, indicating that MMP-9 plasma levels do not specifically reflect CU activity. Most notably, total and active MMP-9 levels were not correlated with disease activity in CU. |
| 51 | Asero et al (2008) | F1+2<br>D-dimer | In patients with severe CU, median levels of both D-dimer (11.20 nmol/l) and F1+2 (592 pmol/l) largely exceeded those found in patients with slight CU [D-dimer: 2.66 nmol/l (p = 0.001) and F1+2: 228 pmol/l (p = 0.003)] and in normal subjects. D-dimer and F1+2 levels significantly correlated with each other (r = 0.64, p = 0.002) and with CU severity score (r = 0.80-0.90, p = 0.0001). |
| 52 | Tedeschi et al (2008) | IL-18 | Serum IL-18 concentration was not significantly different between patients with chronic ordinary urticaria and normal subjects, and no significant difference was found between ASST-positive and ASST-negative patients. |
| 53 | Asero et al (2008) | F1+2<br>D-dimer<br>FXII<br>FVII<br>TF | Mean F1+2 levels were higher in patients than controls (p < 0.001); disease activity was moderate or severe in 9 of 11 (82%) and 9 of 26 (35%) patients showing high or normal F1+2 levels, respectively (p < 0.025). Mean D-dimer plasma levels were higher in patients than controls (p < 0.01); disease activity was moderate or severe in 6 of 8 (75%) and 11 of 29 (38%) showing elevated or normal plasma D-dimer levels (p = not significant). Factor VIIa levels were higher in patients than controls (p < 0.001). Activated factor VII and F1+2 levels were correlated (p = 0.008). Tissue factor reactivity was observed only in CU skin specimens. |
| 54 | Kasperska-zajac et al (2007)[5] | MnSOD<br>Cu/ZnSOD<br>GSH-Px<br>catalase<br>MDA | The antioxidative enzyme activity in plasma (CuZn/SOD and MnSOD) and in erythrocytes (CuZn/SOD,GSH-Px, and CAT) as well as plasma and erythrocyte level of MDA did not differ significantly between chronic inducible urticaria patients and the healthy subjects (exact data not given in article). |
| 55 | Kasperska-zajac (2007)[6] | u-PAR<br>su-PAR<br>PAI-1 activity | The plasma level of u-PA and suPAR antigens, PAI-1 activity did not differ significantly among the three subjects groups. The data obtained suggest that CU patients showing positive response to ASST have plasma profile of the urokinase system-associated proteins, which is not markedly different as compared with CU patients with negative ASST as well as healthy subjects. |

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| 56 | Miyazaki et al (2006) | P-selectin<br>TNF-α | Histamine rapidly induced P-selectin expression. IL-4 and IL-13 induced prolonged expression of surface P-selectin by HDMECs. A combination of TNF-α and IL-4 inhibited P-selectin expression. Pre-treatment of HDMECs with TNF-α followed by incubation with IL-4 markedly increased P-selectin expression. Notably, incubation with substance P alone induced prolonged P-selectin expression. Activation of STAT6 appears to be a key factor in P-selectin expression induced by substance P and IL-4 because treatment with STAT6 decoy oligodeoxynucleotides significantly inhibited P-selectin expression. |
| 57 | Szegedi (2006) | sCD40L | The serum level of sCD40L was significantly higher in CU patients compared with controls, but the difference between the autoimmune and the nonautoimmune groups was not significant. |
| 58 | Asero et al (2006) | F1+2 | Plasma F1+2 was higher in patients than controls ($p < 0.001$) and in ASST-positive/APST-positive than in ASST-negative/APST-positive patients ($p = 0.058$) and was directly related to urticaria severity ($r = 0.37$; $p < 0.05$). |
| 59 | Cassano et al (2006) | ROS<br>SOD | Radical oxygen species concentrations and SOD activity were significantly elevated in patients with chronic idiopathic urticaria at baseline as compared with control subjects. |
| 60 | Caproni et al (2006)[7] | IL-4<br>IL-5<br>IL-8<br>ICAM<br>VCAM<br>E selectin<br>IFN-γ | ICAM-1, VCAM and E-selectin have shown a significantly major expression in spontaneous lesions in comparison to induced weals. IL-5 staining showed a major expression in spontaneous weals when compared to serum-evoqued weals. IFN-γ, although more represented in urticaria spontaneous lesions, showed low levels in both wheals. IL-4 positive cells in serum-evoked lesions outnumbered at 30' the mean count in spontaneous ones. Il-8 was also more present in spontaneous than in induced lesions, with significant difference at 10' ($p = 0,01$). |
| 61 | Caproni et al (2006)[8] | ICAM-1<br>VCAM-1<br>E-selectin<br>P-selectin | After levocetirizine therapy CAM levels decreased in patients with CU, significantly in the cases of E-selectin and P-selectin. Patients' clinical scores improved during regular antihistamine therapy. |
| 62 | Tedeschi et al (2006) | TNF-α | TNF-α concentration was below the sensitivity of the assay (15,6 pg/ml) in all serum samples from chronic urticaria patients and normal subjects. |
| 63 | Tedeschi et al (2005) | Substance P | Mean serum substance P concentration was not significantly different in contact urticaria patients and in normal subjects. Mean serum substance P concentration did not vary significantly in the different subsets of patients. |

**Supplementary file III. Summary of all 79 selected articles**

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| 64 | Kessel et al (2005) | MMP-9 | Plasma levels of MMP-9 were found to be significantly higher in 29 CU patients compared with 18 healthy controls ($p < 0.0001$). We also found a significant correlation between MMP-9 levels and urticarial severity ($r = 0.92$, $p < 0.001$). |
| 65 | Caproni et al (2005) | IL-4<br>IL-5<br>IL-8<br>ICAM-1<br>VCAM<br>E-selectin<br>IFN-γ | IFN-γ and IL-5 were expressed focally in autologous wheals. Significant staining for IL-4 was seen at 30'. CCR3 and CXCR3 were expressed less in autologous wheals than in uninvolved skin ($p < 0.0001$; $p = 0.002$). Cellular adhesion molecules reached their highest expression at 30' and 60' in induced lesions, and they showed strong expression also in unaffected skin (ICAM-1: $p < 0.0001$). |
| 66 | Caproni et al (2003) | IL-4<br>IL-5<br>IL-8<br>IFN-γ<br>ICAM-1<br>VCAM-1<br>E-selectin | A significant expression for IL-4 and IL-5 could only be observed in lesional skin, while IFN-γ showed a slight expression in the same site. An increased expression of all cellular adhesion molecules studied was detected in spontaneous wheals. The lack of a significant difference in the expression of IL-8 and a few CAMs between the lesional and unaffected skin of chronic idiopathic urticaria patients suggests a wide immunological activation that involves not only lesional tissues, but possibly extends to the whole of the skin's immune system. |
| 67 | Raho et al (2003) | SOD<br>Glutathione<br>MDA | The activity of SOD and glutathione and the levels of MDA were markedly increased in lesional skin as compared with skin of healthy subjects, whereas no differences were detected between non-lesional skin of chronic idiopathic urticaria patients and control samples. Immuno-dot blot assay revealed an upregulation of Mn-SOD expression in lesional skin. |
| 68 | Asero et al (2003) | SCF | Serum SCF levels in all 65 chronic idiopathic urticaria patients did not differ from those found in healthy controls. No difference in SCF levels was found between patients with positive and negative results on histamine release assay. |
| 69 | Lee et al (2002) | ICAM-1<br>VCAM-1<br>E-selectin<br>TNF-α | TNF-α increased significantly in foreskin mast cell culture challenged with sera of chronic urticaria patients. After the stimulation of HDMECs with the conditioned media, the expression of ICAM-1, VCAM-1, and E-selectin increased significantly. Treatment of the conditioned media with anti-TNF-α monoclonal antibody partially inhibited the expression of ICAM-1,VCAM-1, and E-selectin. |

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| 70 | Briganti et al (2001) | catalase<br>GSH-Px<br>SOD | Compared with controls, a systemic imbalance of the antioxidants was detected in the CU group with a decrease of both plasma vitamin E and cellular catalase and GSH-Px activities along with an increase of SOD activity. Moreover, an increase in the percentage of plasma polyunsaturated fatty acids, as a target for peroxidative damage, was also observed. These alterations may lead to an increased percentage of peroxidable compounds in skin and to the intracellular generation of reactive oxygen species and could therefore provide one possible explanation for the patients' urticarial response to stimuli. |
| 71 | Hermes et al (1999) | IL-3<br>IL-8<br>TNF-α | Compared with normal skin and prick test reactions, immunoreactivity for TNF-α and IL-3 was significantly increased on endothelial and perivascular cells of the upper dermis in all urticaria lesions. In non-lesional skin comparable upregulation was noted on ECs and for TNF-α on perivascular cells of patients with delayed pressure urticaria. In addition, TNF-α was expressed throughout the epidermis in lesional and non-lesional skin of patients with all types of urticaria, but not in normal control subjects. Sequential biopsy specimens from patients with cold urticaria showed upregulation of TNF-α and IL-3 on ECs 30 minutes after elicitation of lesions with an ice cube. In contrast to these findings, epidermal immunoreactivity, as well as endothelial and perivascular cell expression of IL-8, were only slightly altered in urticaria compared with normal skin. In sequentially stained sections, few tryptase-positive mast cells reacted to TNF-α, few reacted to IL-3 in pressure urticaria only, and practically none stained for IL-8. |
| 72 | Haas et al (1998) | E-selectin<br>ICAM-1<br>P-selectin | In wheals of ≤ 30 min duration, no increase of E-selectin and ICAM-1 was noted. P-selectin expression was absent in prick tests, but could be demonstrated in lesions of cholinergic and cold urticaria, with a gradual increase of the latter with time. In wheals of ≥ 6 h duration, P-selectin was only weakly expressed whereas E-selectin and ICAM-1 were markedly up-regulated in lesional and less so in non-lesional skin of acute, chronic recurrent and delayed pressure urticaria. |
| 73 | Hermes et al (1997) | CD40L | Compared to normal skin, cells expressing CD40 and CD40L were increased in the dermis, partly also in the epidermis, from patients with atopic dermatitis and scabies, but not in chronic urticaria. CD40 and CD40L were detected on numerous cells in lymphatic tissue from both normal donors and a patient with atopic dermatitis, whereas large numbers of IgE- and Fc epsilon RI-positive cells were only found in the dermopathic lymph node from the atopic dermatitis patient, in contrast to very few in normal lymphatic tissue. |
| 74 | Werfel et al (1997) | C5a | No binding of the C5aR-specific antibodies was detectable in weal and flare reactions which had appeared between 30 and 60min prior to biopsy during the course of chronic idiopathic urticaria. |
| 75 | Zuberbier et al (1997) | E-selectin<br>P-selectin<br>ICAM-1<br>VCAM-1 | A significant increase ($p < 0.01$) was observed for soluble P-selectin in dermographic urticaria and chronic urticaria compared to healthy controls. In contrast, the other adhesion molecules were not significantly elevated in both urticaria groups. Immunohistologically, a strong expression of P-selectin was found in superficial vessels of lesional and non-lesional skin in dermographic urticaria with only a mild increase of the other adhesion molecules studied. |

**Supplementary file III. Summary of all 79 selected articles**

| | | | |
|---|---|---|---|
| 76 | Haas et al (1995) | fibronectin | Prick test weals (of 10 min duration) to common inhalant allergens showed only a minor increase of CD18, whereas in a case of cold urticaria CD11b and CD18 molecules were increasingly upregulated within the first 30 min after elicitation of the lesions. Skin test sites in delayed pressure urticaria, and urticarial lesions (> 6 h duration) of acute and chronic recurrent urticaria also showed marked upregulation of CD11b and CD18, and to a lesser extent of CD11a, but this did not strongly correlate with the intensity of the mixed cellular infiltrate. Non-lesional skin showed expression of beta 2-integrins in chronic urticaria, delayed pressure urticaria, and less so in acute urticaria, suggesting generalized leucocyte activation. |
| | | iC3b | |
| 77 | Barlow et al (1994) | E-selectin | There was moderate to marked upregulation of E-selectin at 6 and 24 h after application of pressure. At 24 h, more patients showed expression of VCAM-1 on perivascular cells than before pressure. Moderate expression of ICAM-1 was present in some biopsies from both unchallenged and pressure-challenged skin, but there was no clear trend. |
| | | ICAM-1 | |
| | | VCAM-1 | |
| 78 | Czarnetzki et al (1989) | MIF | Positive staining of upper and mid-dermal dendritic cells was noted in sections from all three biopsy specimens of acute urticaria, eight of chronic urticaria, and all six of urticaria pigmentosa lesions. In all but one biopsy specimen, ECs reacted as well. In three sections (two chronic urticaria, one urticaria pigmentosa), luminal lining cells of sweat glands were also noted to stain positively. In contrast, lesional skin from all eight patients with pressure urticaria was negative, as was the clinically normal skin of all patients, with the exception of one patient with urticaria pigmentosa. |
| 79 | Bork et al (1984) | C4 | C4 levels in urticaria patients were not significantly higher than in patient group with hereditary angioneurotic edema. Factor XII, HMWK, XI, VIII and V levels were significantly raised in 10 patients with frank chronic urticaria, while factor VII was lowered. Several urticaria patients had short (but not significantly decreased) PTT values. |
| | | FXII | |
| | | HMWK | |
| | | FXI | |
| | | FVIII | |
| | | FV | |

*Table legend: data is given as results of all 79 selected articles classified according to described biomarker and/or relevant process of EC dysfunction in CU pathogenesis.*

[1] Indian J of Dermatol

[2] Ann Allergy Asthma Immunol

[3] Int Arch Allergy Immunol

[4] Cytokine

[5] Kasperska-Zajac A, Brzoza Z, Rogala B. Blood urokinase plasminogen activator system in chronic urticaria. Arch Dermatol Res. 2007;298(8):409-11.

[6] Kasperska-Zajac A, Brzoza Z, Polaniak R, Rogala B, Birkner E. Markers of antioxidant defence system and lipid peroxidation in peripheral blood of female patients with chronic idiopathic urticaria. Arch Dermatol Res. 2007;298(10):499-503

[7] Int J Immunopathol Pharmacol.

[8] Br J Dermatol.

*Abbreviations in table: ADP: adenosine diphosphate; AICU: aspirin-intolerant chronic urticaria; AGE: advanced glycation end products; Ang II: angiotensin II; APST: autologous plasma skin test; aPTT: activated partial thromboplastin time; α2- APL: α2-antiplasmin; ASST: autologous serum skin test; AT III: antithrombin; ATCU: aspirin-tolerant chronic urticaria; AU: acute urticaria; BP:*

**Supplementary file III. Summary of all 79 selected articles**

*blood platelets; BPs: blood platelets; C1 est inh: C1 esterase inhibitor; C3: complement C3; C4: complement C4; C5a: complement C5a; CCL: chemokine (C-C) ligand; CD: cluster of differentiation; CD40L: cluster of differentiation 40 ligand; cGRP: calcitonine gene-related peptide; cHK: cleaved high molecular weight kininogen; CS: complement system; CSU: chronic spontaneous urticaria; CuZnSOD: copper-zinc dismutase; Cu: copper; CU: chronic urticaria; DPU: delayed pressure urticaria; EC: endothelial cell; ECs: endothelial cells; ECP: eosinophil cationic protein; F1+2: prothrombin fragment 1+2; FI: factor I; FII: factor II; FV: Factor V; FVIII: factor VIII; FIX: factor IX; FX: factor X; FXI: factor XI; FXII: factor XII; FVIIa: activated factor VII; FDP: fibrin degradation products; fMLP: N-formyl-l-methionyl-l-leucyl-phenylalanine; GSH-Px: glutathione peroxidase; HDMEC-1: human dermal microvascular endothelial cells; HMWK: high molecular weight kininogen; hsp-70: heat shock protein 70; ICAM: intercellular adhesion molecule; iC3b: Inactivated complement 3b; IFN-γ: interferon gamma; IL-: interleukin- ; IL-6 sR : interleukin 6 soluble receptor ; L: lesional; MDA: malondialdehyde; LCN2: lipocalin-2; MIF: migration inhibitory factor; miR-125a-5p: micro-RNA-125a; MMP: matrix metalloproteinases; MnSOD: manganese superoxide dismutase ; MPV: mean platelet volume; Nb: number; NL: non-lesional; P2Y12: adenosine diphosphate chemoreceptor; PDW: platelet distribution width; PECAM: platelet endothelial cell adhesion molecule; PT: prothrombin time; PUFA: plasma phospholipid fatty acid; RAGE: receptor for advanced glycation end product; ROS: reactive oxygen species; SCF: stem cell factor; SFMC: soluble fibrin monomer complex; sgp130: soluble gp130; SOD: superoxide dismutase; sRAGE: soluble receptor for advanced glycation end product; su-PAR: soluble urokinase-type plasminogen activator receptor; sVE-cadherin: soluble vascular endothelial cadherin; S100A8/9/12: S100 calcium and zinc-binding protein A8/9/12; TAS: total anti-oxidant status; TAT: thombin-antithrombin complex; TF: tissue factor; TFPI/Xa: tissue factor pathway inhibitor/activated factor Xa; TG2: transglutaminase 2; TGF-β: transforming growth factor beta; TM: thrombomodulin; TNF-α: tumor necrosis factor alpha; TOS: total oxidant status; t-PA: tissue-type plasminogen activator; TRAP: thrombin receptor-activating peptide; TSLP: thymic stromal lymphopoietin; TSP-1: thrombospondin-1; TT: thrombin time; UAS: urticaria activity score(s); UEA-1: ulex europaeus-I lectin; u-PAR: urokinase-type plasminogen activator receptor; USS: urticaria severity score(s); VCAM: vascular adhesion molecule; VE: vascular endothelial;; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; Vit E: vitamin E; vWF: von Willebrands factor; VWF:Ag: von Willebrand factor antigen; YKL-40: chitinase-3-like protein 1; Zn: zinc.*