

# **Study of Regulatory T-cell Percentages in Peripheral Blood of Patients with Chronic Urticaria**

***Thesis***

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# دراسة نسب الخلايا التائية التنظيمية في المصل لدى مرضى الأرتيكاريا المزمنة

رسالة

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# قالوا

لَسْبَدَانِكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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## *List of abbreviations*

<b>ACE</b>	<i>Angiotensin-converting-enzyme</i>
<b>ACEI</b>	<i>Angiotensin-converting-enzyme inhibitor</i>
<b>ACU</b>	autoimmune chronic urticaria
<b>Ag</b>	Antigen
<b>AITD</b>	Autoimmune Thyroid Disease
<b>AMA ABs</b>	Anti microsomal antibodies
<b>ANA</b>	Anti-nuclear antibody
<b>Anti TgAB</b>	Anti thyroglobulin anti bodies
<b>anti-IgE</b>	Anti Immunoglobulin E
<b>Anti-TPO antibody</b>	Anti thyroperoxidase antibodies
<b>APC</b>	Antigen-presenting cells
<b>ARBS</b>	Angiotensin II Receptor Blockers
<b>ASST</b>	Autologous skin sensitivity test
<b>aTreg</b>	adaptive T-regulatory
<b>Auto Ag</b>	Autoantigen
<b>BAFF</b>	B-cell activating factor
<b>BSACI</b>	British Society for Allergy and Clinical Immunology
<b>C</b>	Complement
<b>C1-INH</b>	C1-esterase inhibitor
<b>cAMP</b>	Cyclic adenosine monophosphate
<b>CAU</b>	Chronic auto immune urticaria
<b>CBC</b>	Complete blood count
<b>CCL</b>	CC chemokine ligand
<b>CCR</b>	C-C motif receptor, beta chemokine receptor
<b>CD</b>	Cluster of differantiation
<b>CIU</b>	Chronic Idiopathic Urticaria
<b>COX</b>	Cyclooxygenase
<b>CRP</b>	C - reactive protein
<b>CSU</b>	Chronic spontaneous Urticaria
<b>CTLA</b>	Cytotoxic T lymphocyte antigen
<b>CU</b>	Chronic Urticaria
<b>CXCR</b>	CXC chemokine receptors



<b>DC</b>	Dendritic cell
<b>DIT</b>	Diiodo-tyrosines
<b>DNA</b>	Deoxyribonucleic acid
<b>ECP</b>	Eosinophilic cationic protein
<b>ELISA</b>	Enzyme linked immunosorbant assay
<b>ESR</b>	Erythrocyte sedimentation rate
<b>FC receptors</b>	(Fragment, crystallizable) region
<b>FcεRI</b>	Fc epsilon RI
<b>FITC</b>	Fluorescein isothiocyanate
<b>FKH</b>	Forkhead
<b>Foxo3</b>	Forkhead box O3
<b>Foxp3</b>	Forkhead box P3
<b>FT4</b>	Free T4
<b>GARP</b>	Glycoprotein A repetitions predominant
<b>GATA</b>	Globin transcription factor
<b>GITR</b>	Glucocorticoid-induced TNFR-related protein
<b>GLyCAM</b>	Glycosylation-dependent cell adhesion molecule
<b>HAE</b>	Hereditary angioedema
<b>HBsAg</b>	Hepatitis B surface antibody
<b>HCV Ab</b>	Hepatitis C virus antibody
<b>HDAC</b>	histone deacetylase
<b>HEVs</b>	High endothelial venules
<b>HIF</b>	Hypoxia-inducible factor
<b>HLA-DR</b>	Human leukocyte antigen DR
<b>HPT</b>	Hypothalamic/pituitary/thyroid
<b>H-pylori</b>	<i>Helicobacter pylori</i>
<b>HRA</b>	histamine-releasing assays
<b>HSP</b>	Heat shock protein
<b>HTN</b>	Hypertension
<b>ICOS</b>	Inducible T cell co-stimulator
<b>IFN -γ</b>	Interferon-gamma
<b>Ig</b>	Immunoglobulin
<b>IGF-1</b>	Insulin-like growth factor I
<b>IL-2Rα</b>	Interleukin-2receptor alpha chain



<b>ILs</b>	Interleukins
<b>IQR</b>	Interquartile range
<b>KAT</b>	Histone acetyltransferase KAT
<b>kDa</b>	Kilo dalton
<b>KFT</b>	Kidney function test
<b>LAP</b>	Leukocyte alkaline phosphatase
<b>LFT</b>	Liver function test
<b>LPR</b>	Late-phase reaction
<b>LTC</b>	Leukotriene C
<b>MAd CAM</b>	Mucosal vascular addressin cell adhesion molecule
<b>MBP</b>	Major basic protein
<b>MC</b>	Mast cell
<b>MIP</b>	Macrophage inflammatory protein
<b>MIT</b>	Monoiodo-tyrosines
<b>MPEC</b>	Long-lived memory cells
<b>NFAT</b>	Nuclear factor of activated T cells
<b>NF-<math>\kappa</math>B</b>	Nuclear factor- $\kappa$ B
<b>NSAIDS</b>	Nonsteroidal anti-inflammatory drugs
<b>nTreg</b>	naturally occurring T-regulatory
<b>P.B.S.</b>	Phosphate-buffered saline
<b>PBMC</b>	Peripheral blood mononuclear cells
<b>PCR</b>	Polymerase chain reaction
<b>PE</b>	Phycoerythrin
<b>PECy5</b>	Phycoerythrin cytochrome
<b>PLC</b>	Phospholipase C
<b>RANTES</b>	Regulated on activation, normal T cell expressed and secreted
<b>Ras</b>	Rat sarcoma
<b>RAST</b>	Radio Allegro Sorbent Test
<b>RNA</b>	Ribonucleic acid
<b>ROG</b>	Repressor of gata
<b>ROR</b>	Retinoic acid receptor-related orphan receptor
<b>RUNX</b>	Runt-related transcription factor
<b>SHIP</b>	SH2-containing inositol phosphatase
<b>SLE</b>	Systemic lupus erythematosus



<b>SPT</b>	Skin prick test
<b>STAT</b>	Signal transducer and activator of transcription
<b>T conv</b>	Conventional human T-regulatory
<b>TA</b>	Thyroid autoantibodies
<b>TBG</b>	Thyroxine binding globulin
<b>TCR</b>	T cell receptor
<b>Teff</b>	T effector
<b>TF</b>	Transcription factor
<b>TFH</b>	Follicular B Helper T cells
<b>Tg</b>	Thyroid gland
<b>TGF</b>	Transforming growth factor
<b>THs</b>	Thyroid hormones
<b>TLR</b>	Toll receptor
<b>TMA</b>	Thyroid antimicrosomal AB
<b>TMB</b>	Tetramethylbenzidine
<b>TNF</b>	Tumor necrosis factor
<b>TNFR</b>	Tumor necrosis factor receptor
<b>TPD</b>	Thyroid antiperoxidase
<b>Treg</b>	T regulatory
<b>TRH</b>	Thyrotropin releasing hormone
<b>TSH</b>	Thyroid stimulating hormone
<b>TSI</b>	<i>Thyroid</i> stimulating immunoglobulin
<b>UAS-7</b>	Urticaria activity score -7
<b>UV</b>	Urticarial vasculitis



## Introduction

Chronic urticaria (CU) is a rather common skin disorder characterized by recurrent, transitory, itchy wheals for more than 6 weeks (*Chen et al., 2008*).

In 80–90% of patients with CU, no specific underlying cause is found, although there is a subset of these patients in whom autoantibodies to the high-affinity IgE receptor FcεRI are found (*Najib and Sheikh, 2009*). This subgroup is labelled chronic autoimmune urticaria (CAU). It was later demonstrated that these antibodies stimulated the release of histamine (*Cherrez et al., 2009*).

In up to 45% of patients with CU, an immediate wheal and flare response to an intradermal injection of autologous serum (autologous serum skin test, ASST) can be demonstrated (*Konstantinou et al., 2009*), suggesting an autoimmune basis for this subset of patients (*Greaves, 2000*). The ASST indicates the presence of circulating histamine-releasing IgG autoantibodies directed against the high affinity IgE receptor FcεRIα present on mast cells and basophils and/or IgE (*Sabroe et al., 1999*).

Examination of biopsies from urticaria patients demonstrated that most of the infiltrating T cells possessed CD4<sup>+</sup> helper phenotype (*Caproni et al., 2003*).

The cytokine pattern reported elsewhere showed that skin biopsies of patients with CU resemble the T-helper

cell type 0 (Th0) cytokine profile with increased levels of interleukin-4, interleukin-5 and interferon-gamma messenger (m)RNA+ cells (*Ying et al., 2002*).

Alternatively, it is also possible that there is a mixture of Th1/Th2 cell types in the skin of patients with CU. These observations support the notion that T lymphocytes and particularly CD4+ T cells are involved in the pathogenesis of CU (*Sun et al., 2011*).

## Aim of the work

The present study aims to measure the frequencies of circulating T-regulatory cells ( $CD4^+$   $CD25^+$   $Foxp3^+$ ) in serum among patients with chronic urticaria, as compared to healthy controls. We further aim to assess the possible relation between frequencies of these cells and the severity of chronic urticaria.