

Immune Response and Hormonal Alterations in C1-inhibitor Deficiency

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Hereditary angioedema

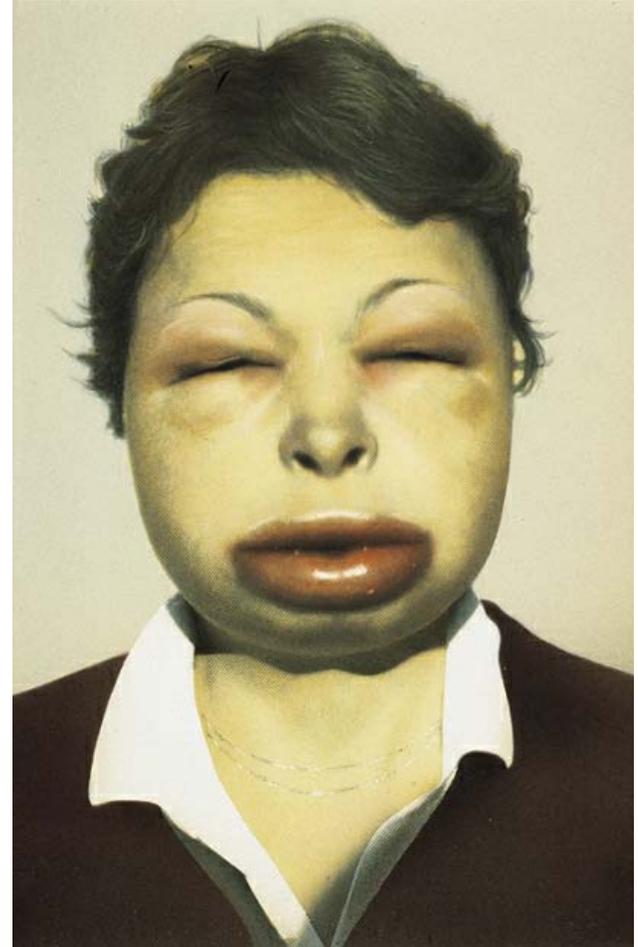
Deficiency of C1 esterase inhibitor (C1-INH) is the most frequent genetic defect of complement system. This inherited defect is responsible for the clinical disorder hereditary angioedema (HAE).

The clinical symptoms of HAE are the result of submucosal and subcutaneous oedema of respiratory tract, gastrointestinal tract and skin.

Hereditary deficiency of C1 inhibitor (C1 INH)

- Congenital deficiency of functional C1 INH
- Clinically manifests as hereditary angioedema
(*Quincke 1882, Osler 1888*)
- C1-INH is central to the regulation of the **complement** coagulation and kinin-forming systems
- **Clinical symptoms:**
swelling,
abdominal attacks,
edema of the upper airway
- **Treatment:**
acute attacks - C1-INH concentrate;

prophylactic - androgens
or antifibrinolytic agents

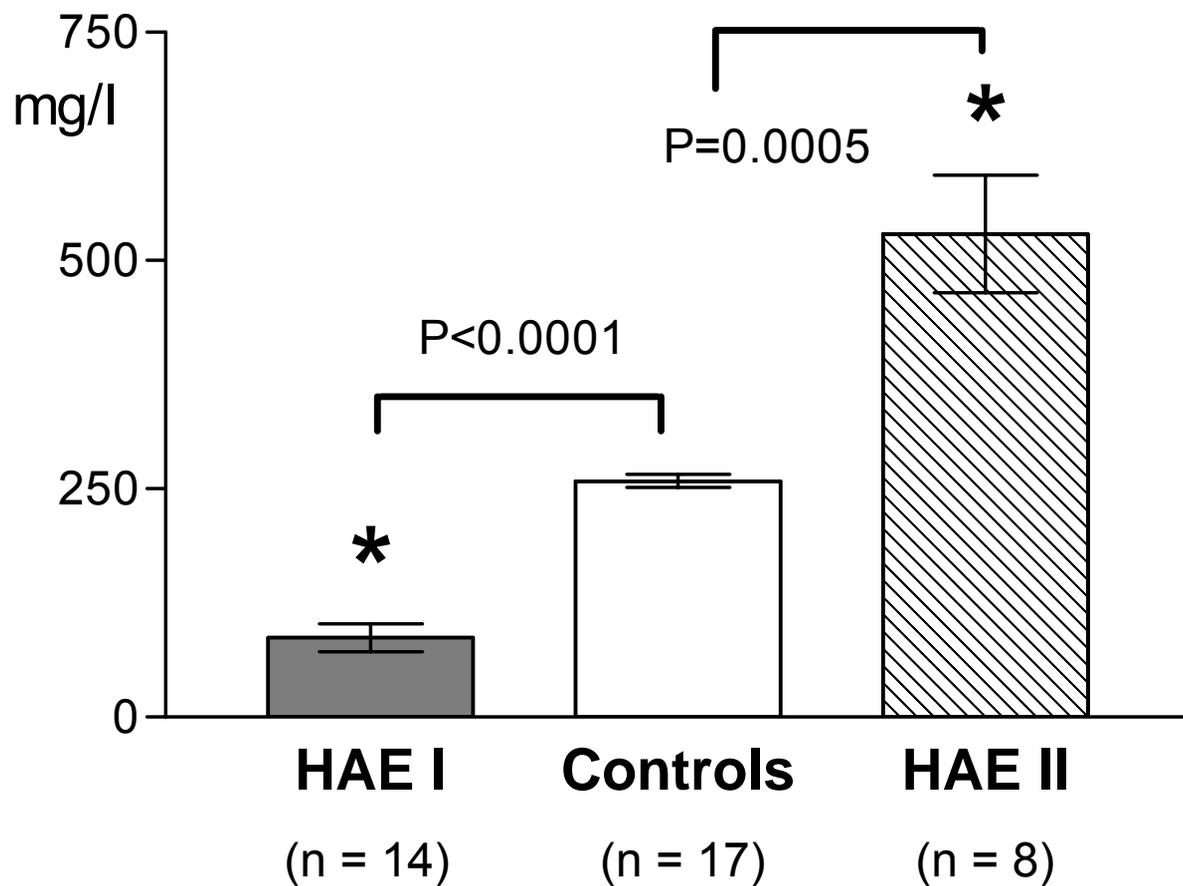


Hereditary angioedema

- In the great majority (at least 85%) of HAE patients plasma levels of C1-INH measured by immunochemical methods are low (HAE I),
- a minority (15% or less) of patients have normal or elevated levels of immunochemical C1-INH but the bulk of the protein is functionally inactive (HAE II).

C1 INH

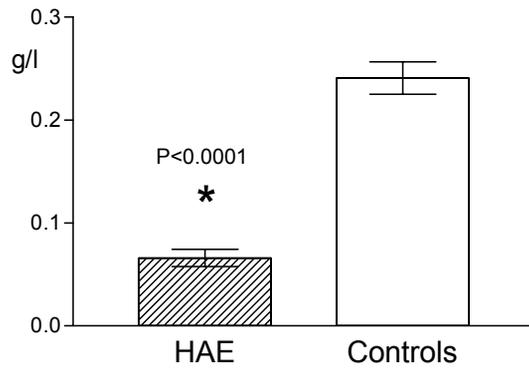
(mean \pm SEM)



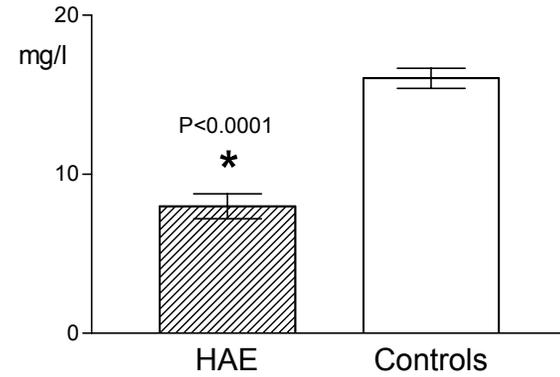
Hereditary angioedema

Inefficiently regulated and chronic low level activation of the classical pathway results in decreased plasma level of C2 and C4 in both types of HAE.

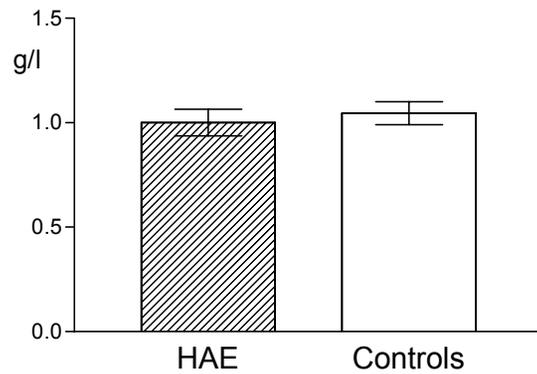
C4
(mean \pm SEM)



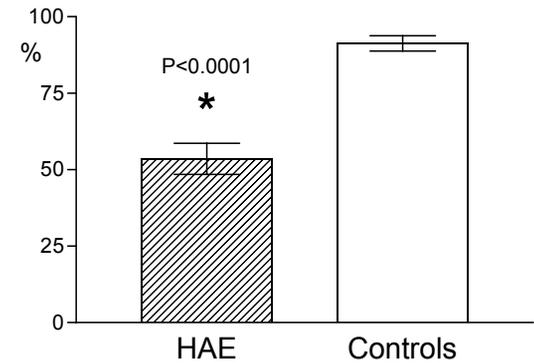
C2
(mean \pm SEM)



C3
(mean \pm SEM)



CH50
(mean \pm SEM)

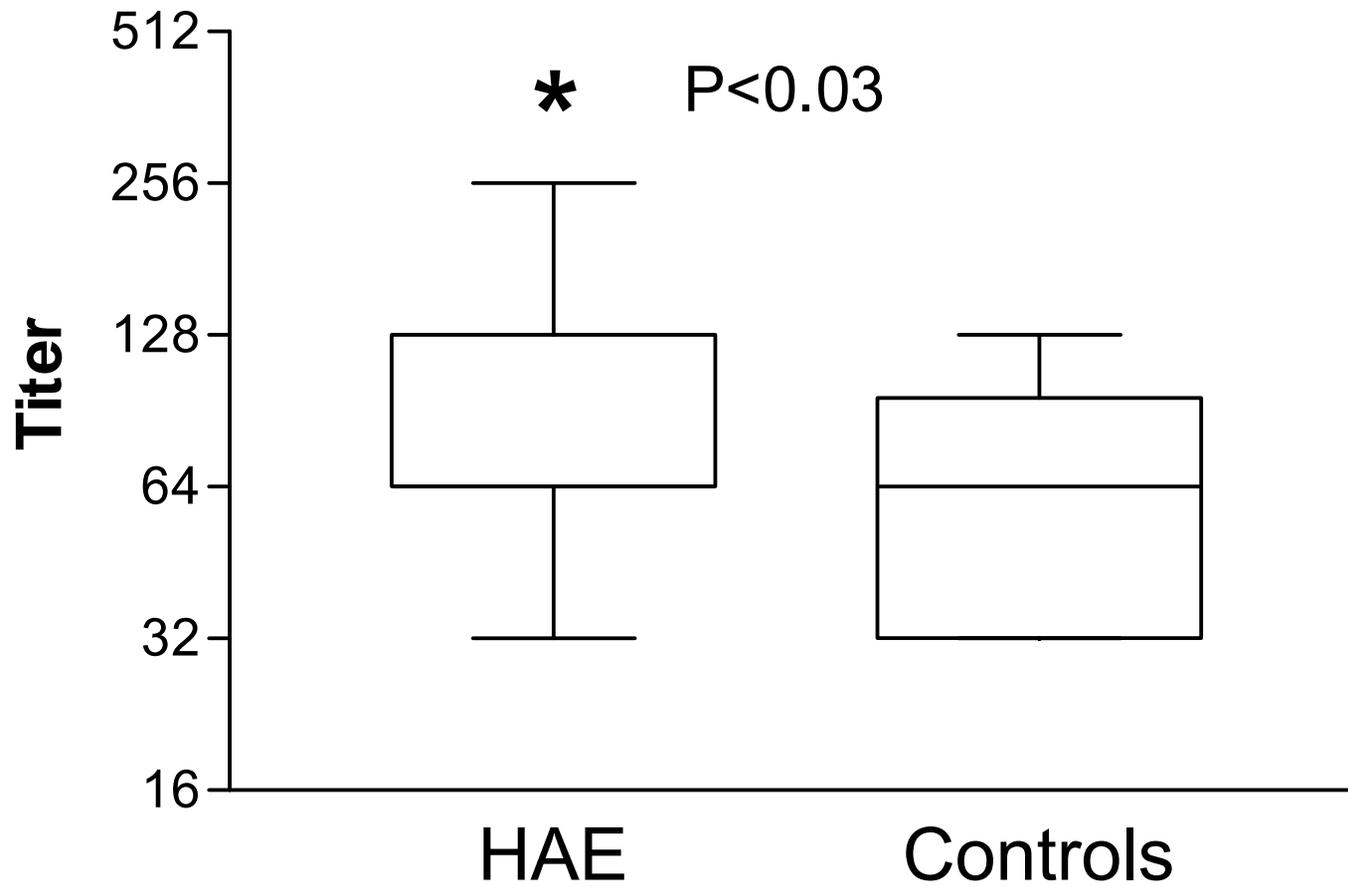


HAE: n = 22 Controls: n = 17

Hereditary angioedema

- The complement system constitutes an important part of the innate immune system, but plays also an important roles in the adaptive immune response: the primary antibody response and/or the formation of immunological memory are dependent on complement and its receptors.

Natural antibodies against rabbit red cells

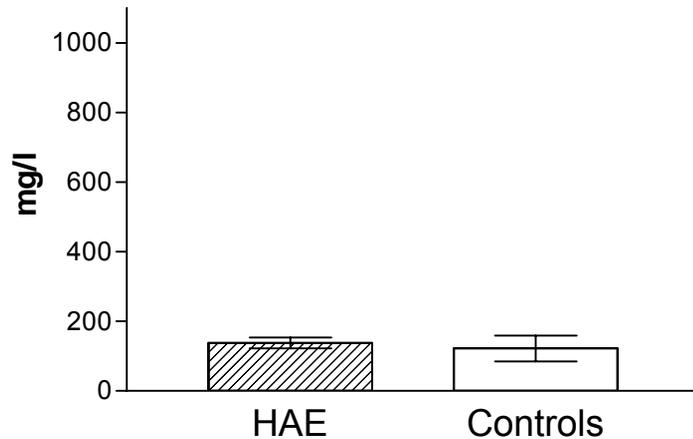


Immune response after antigenic stimulation:

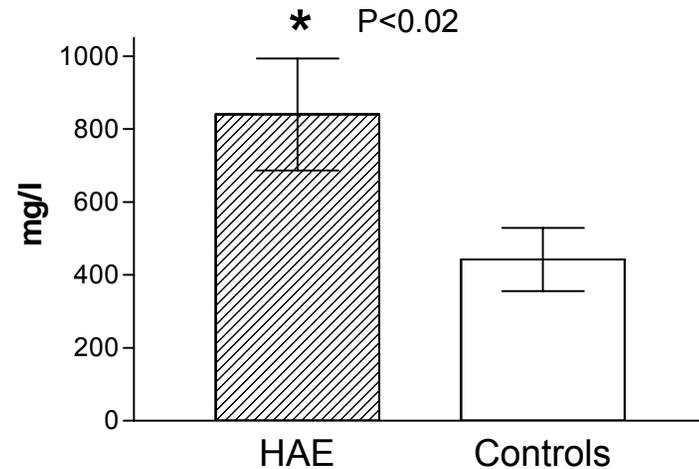
Pneumococcal polysaccharide vaccine

(Pneumo 23 inj., Pasteur Merieux Serum & Vaccines, France)

**anti-PCP Ab
before vaccination**
(mean \pm SEM)

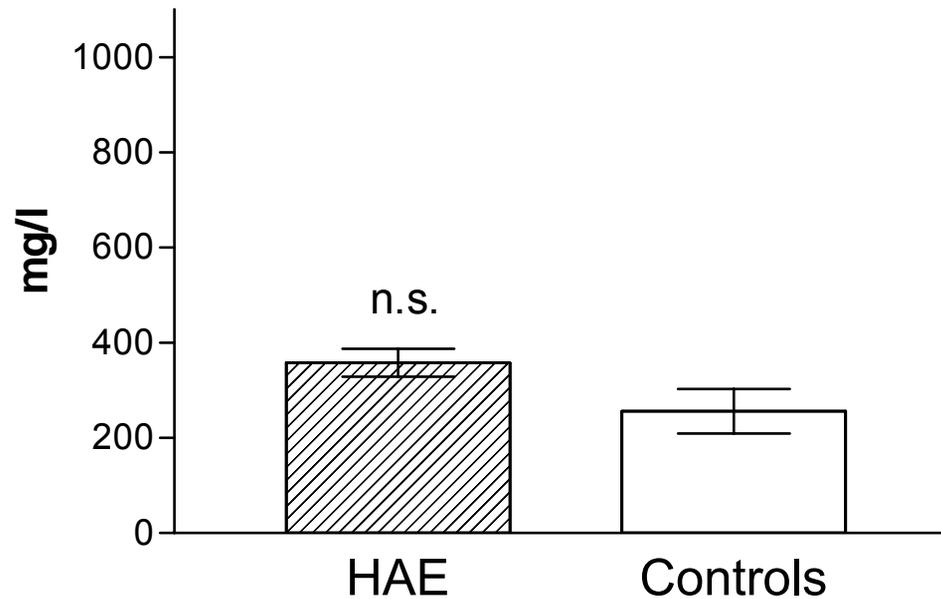


**anti-PCP Ab
3 months after vaccination**
(mean \pm SEM)



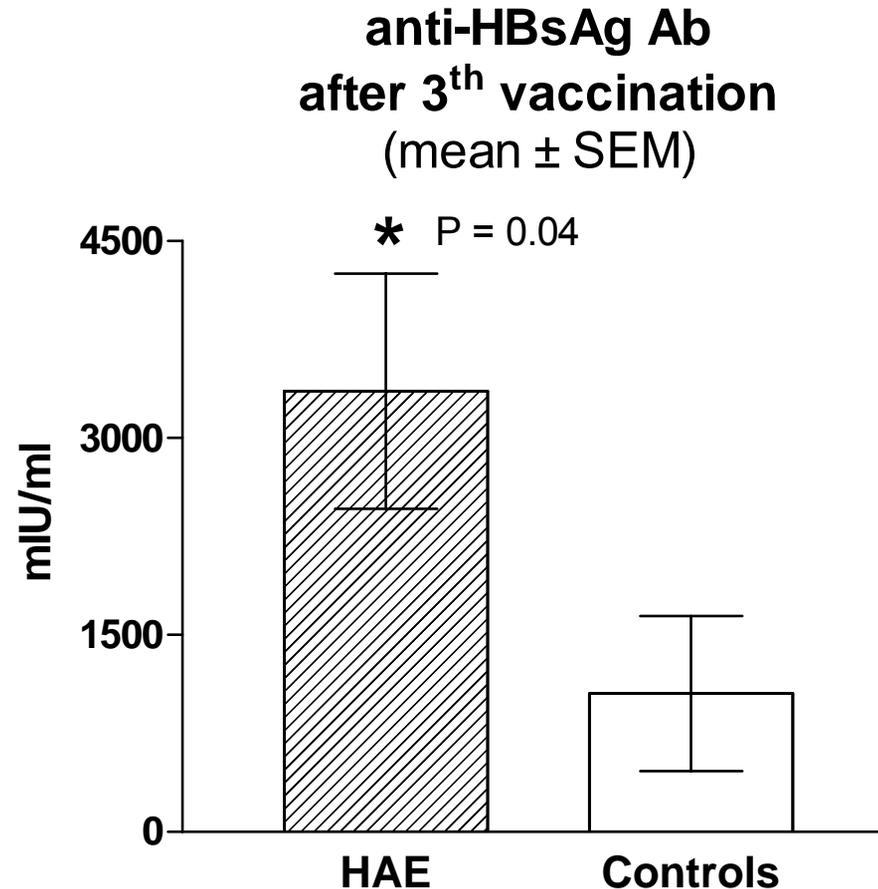
One year later

anti-PCP Ab
1 year after vaccination
(mean \pm SEM)



Immunisation with HBV vaccine

(Engerix B 20 µg inj., SmithKline Beecham Biologicals S.A., Belgium)

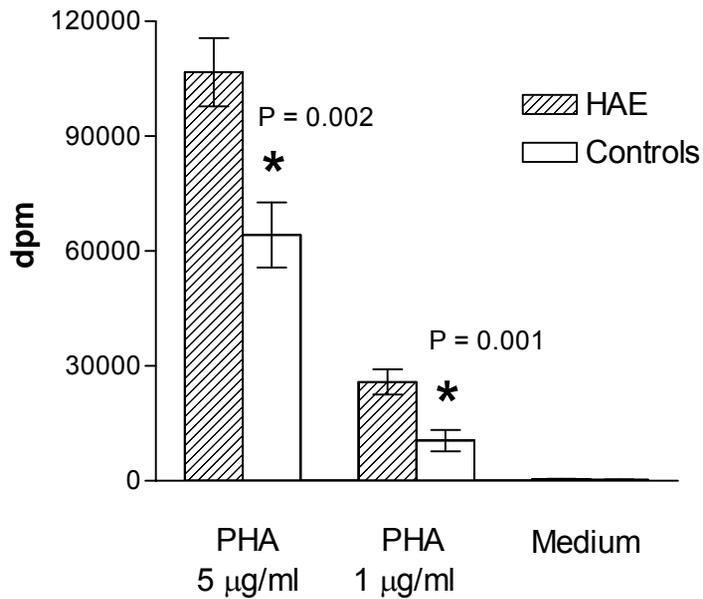


Serum immunoglobuline levels

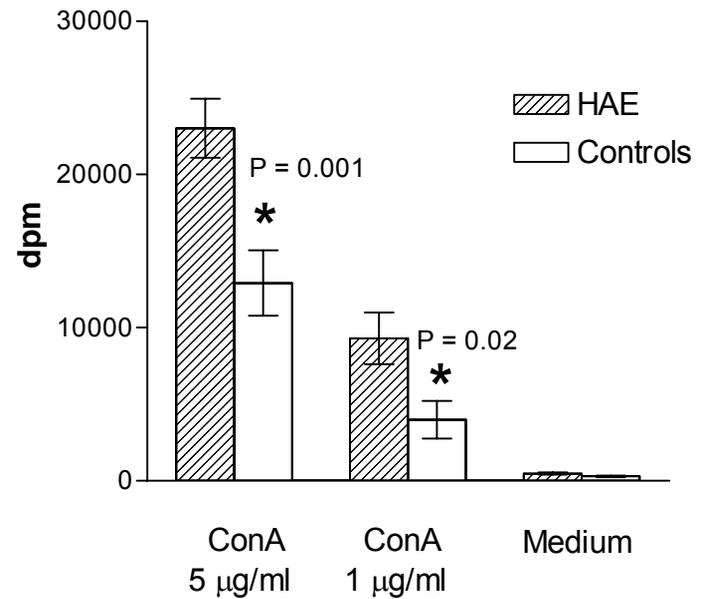
<i>Immunoglobulins</i>	HAE	Controls	P
IgG (g/L)	11,4 ± 1,7	11,3 ± 1,3	0,924
IgA (g/L)	2,2 ± 1,0	2,5 ± 0,8	0,501
IgM (g/L)	1,2 ± 0,4	1,1 ± 0,3	0,581
IgE (IU/mL)	129,3 ± 116,5	133,6 ± 114,1	0,935
IgG1 (g/L)	7,6 ± 1,2	6,9 ± 0,8	0,151
IgG2 (g/L)	4,2 ± 1,7	3,8 ± 1,2	0,553
IgG3 (g/L)	0,5 ± 0,1	0,6 ± 0,2	0,147
IgG4 (g/L)	0,6 ± 0,4	0,5 ± 0,2	0,747

Functional T cell response

Proliferative response
Stimulation with PHA
(PBMNC, mean \pm SEM)

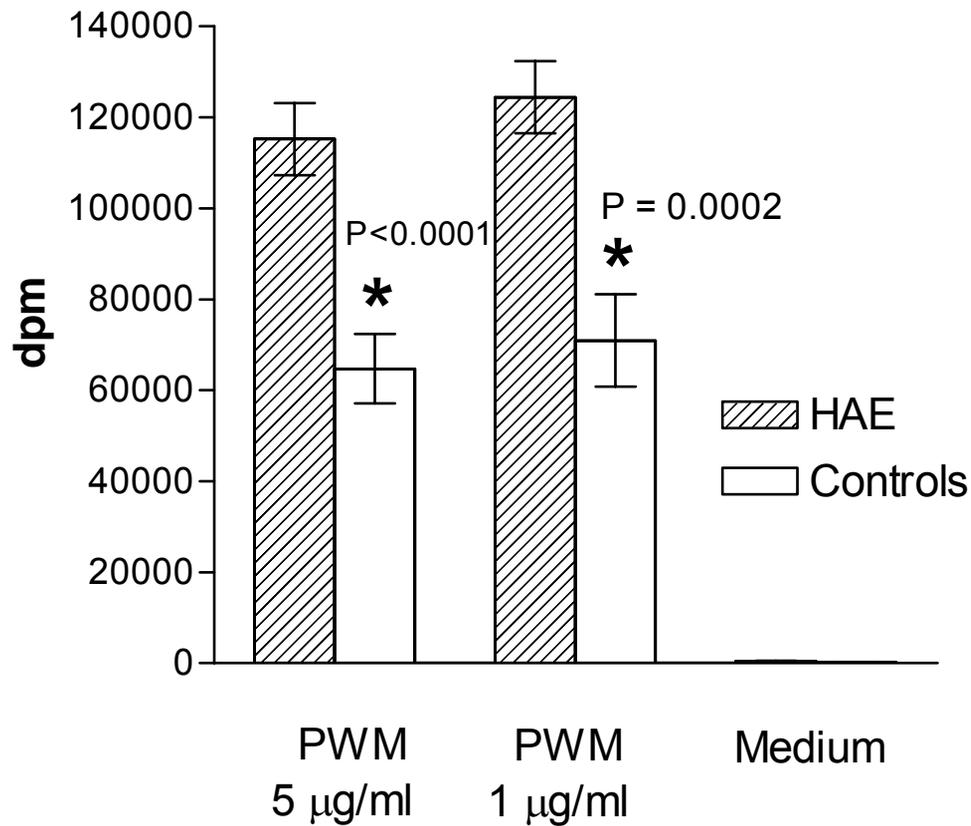


Proliferative response
Stimulation with ConA
(PBMNC, mean \pm SEM)



B cell response

Proliferative response
Stimulation with PWM
(PBMNC, mean \pm SEM)



Immunological response in HAE

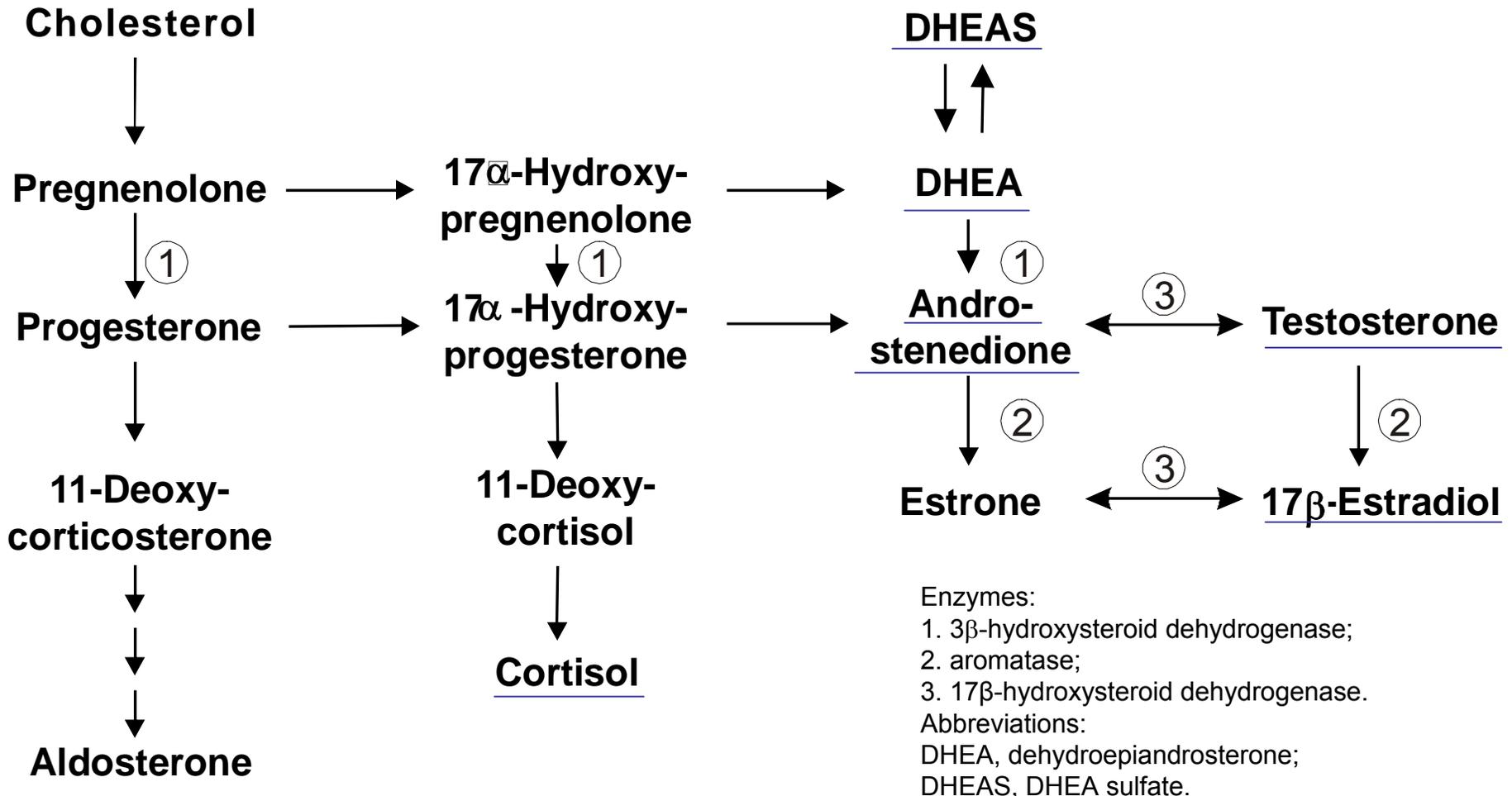
- **We found significantly higher level of the natural antibodies in patient group as well as significantly higher specific antibody response against pneumococcal polysaccharide antigen and HBsAg in HAE patients as compared with controls but occurrence of a panel of autoantibodies was similar.**
- **Moreover, stimulation of peripheral blood mononuclear cells with mitogens (PWM, PHA, ConA) leads to higher proliferative response in HAE patients.**

Hormonal alterations and the role of danazol in steroid hormone conversion

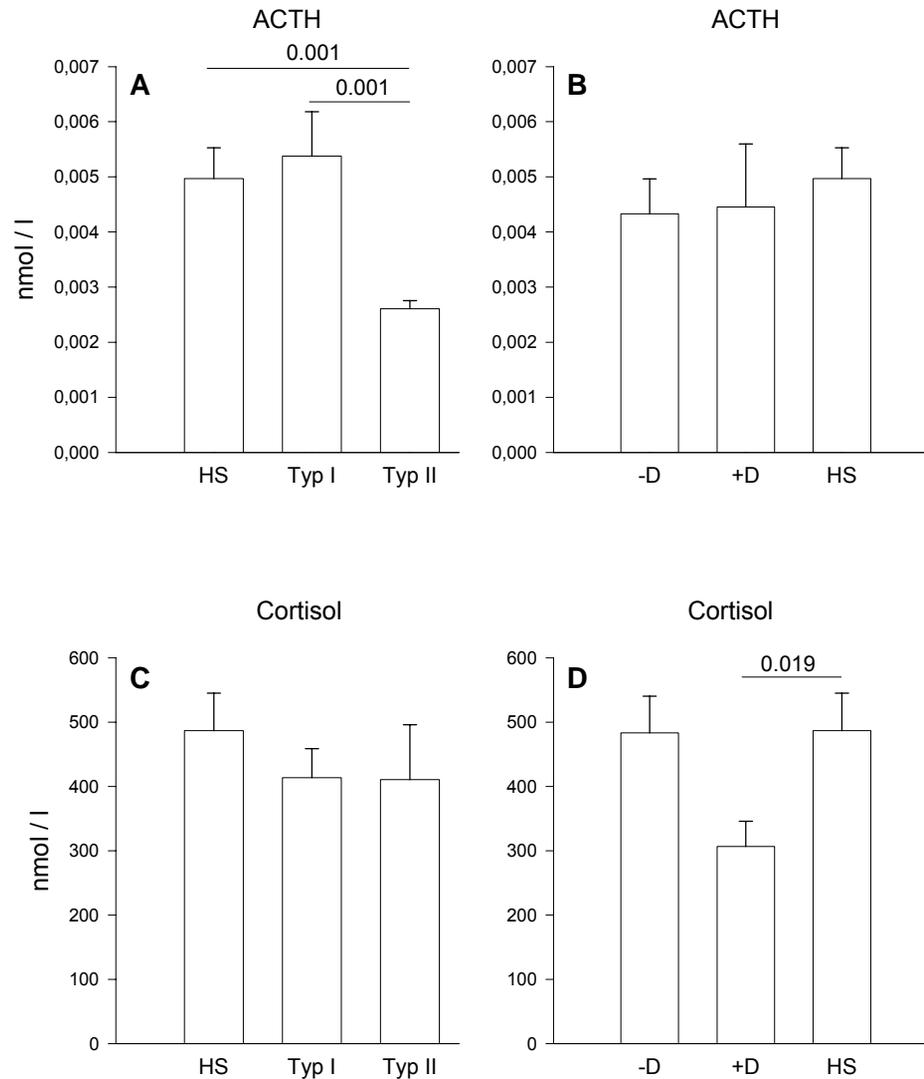
Danazol, an androgenic steroid, is favorable in HAE patients as a long term prophylactic agent.

The status of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axis hormones has never been systematically investigated in a larger group of patients with HAE.

Adrenal and gonadal pathways of steroidogenesis



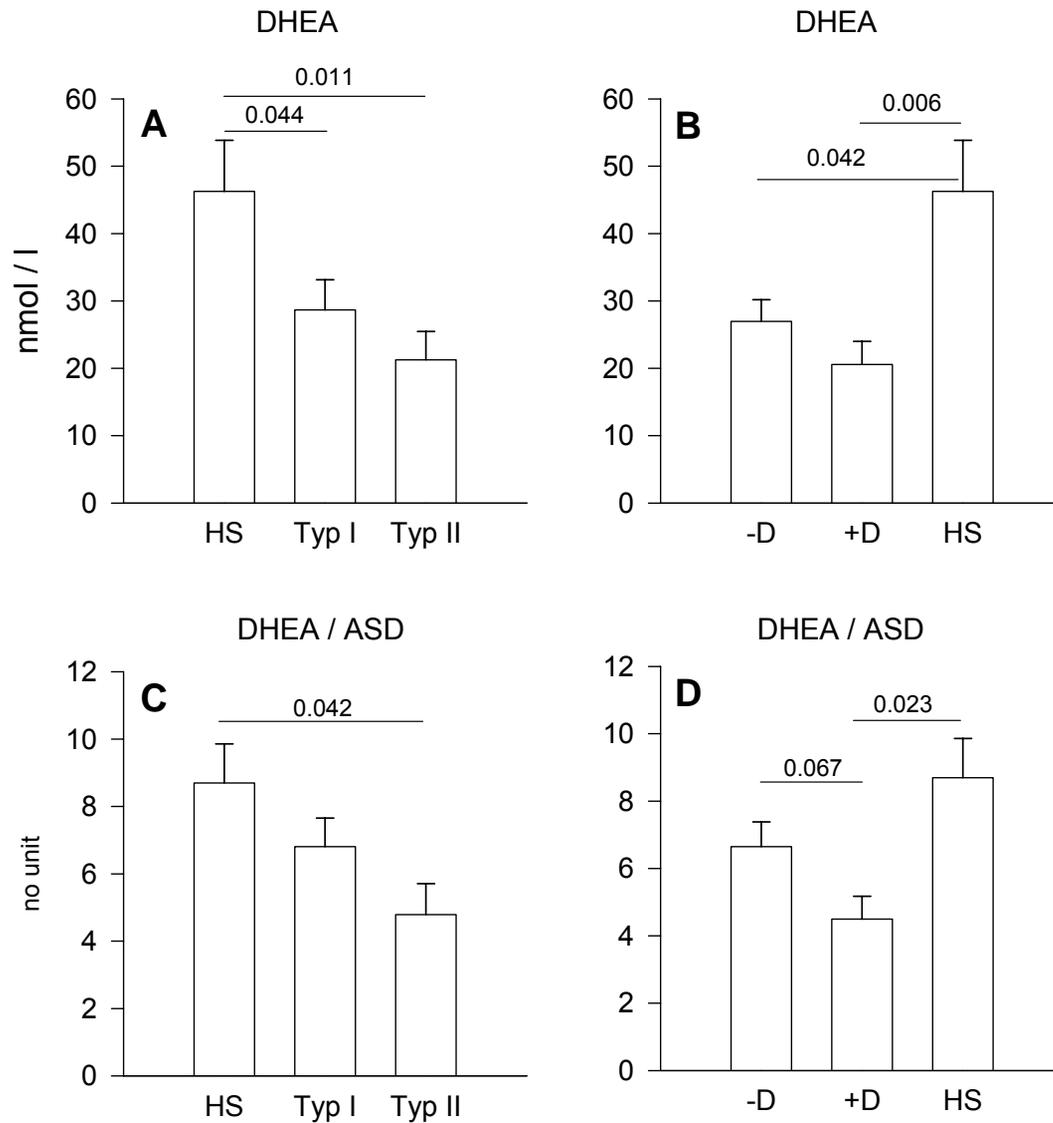
Adrenocorticotrophic hormone and cortisol serum levels in patients with hereditary angioedema



Serum levels of ACTH and cortisol

- Danazol treatment did not change serum levels of ACTH.
- Serum cortisol levels were similar in all groups. However, patients with prior danazol treatment demonstrated lower serum levels of cortisol.

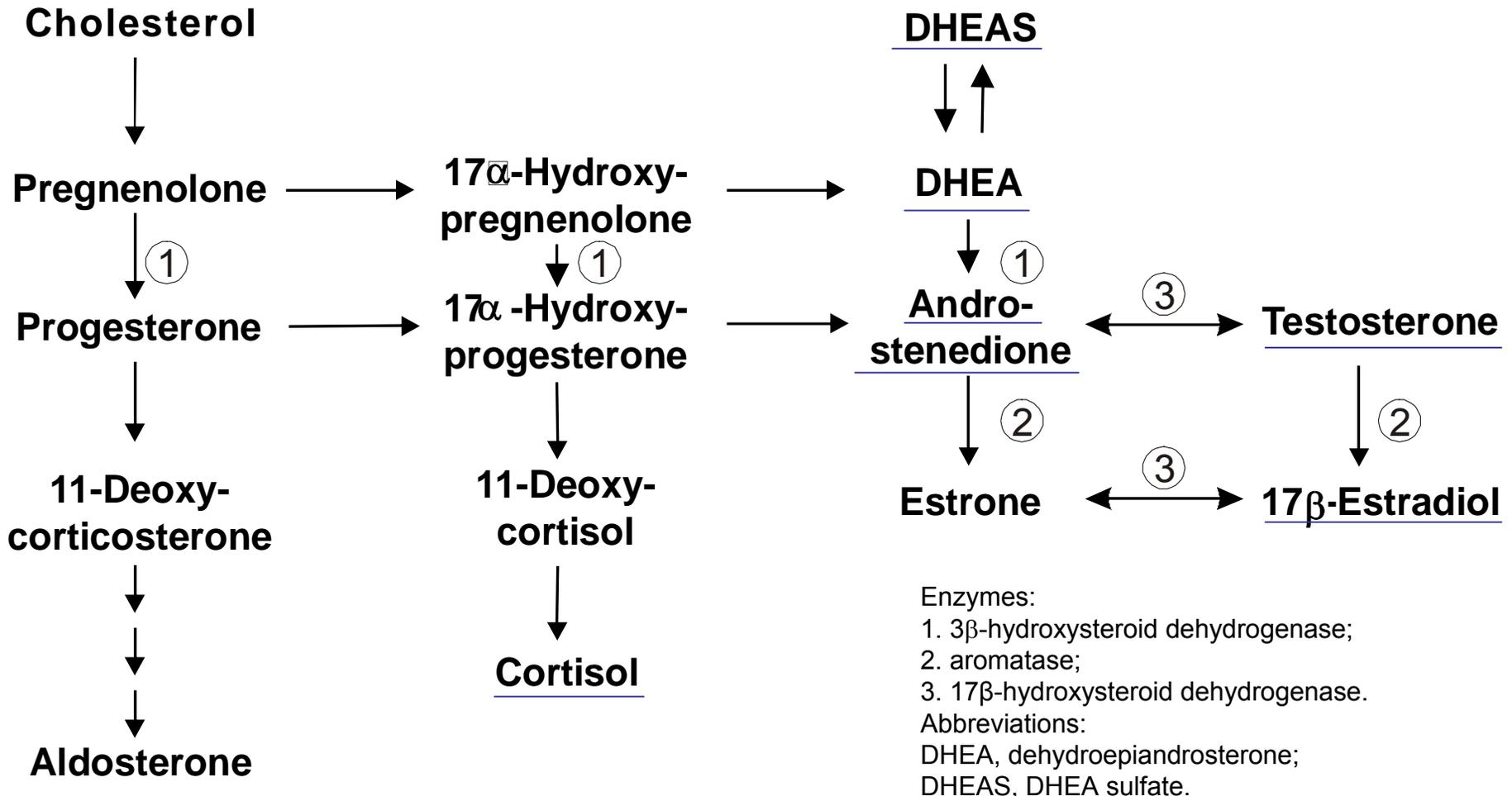
Serum DHEA and the ratio of serum DHEA / androstenedione (ASD) in patients with hereditary angioedema



Hormon conversion

- Serum levels of androstendion were not different.
- It is obvious that danazol treatment was related to a decreased ratio of serum DHEA / serum androstendion. This indicates a danazol-induced increase of DHEA conversion into the direction of androstendion.
- Reduction of DHAЕ is not due to inflammation.

Adrenal and gonadal pathways of steroidogenesis



Comparison of gonadal hormones in patients with and without danazol administration

	healthy subjects	patients without danazol (n = 15)	patients with danazol (n = 10)
serum free testosterone (nmol / l)	0.027 ± 0.007	0.021 ± 0.006	0.070 ± 0.01 ^{†, §}
ratio free testosterone / ASD	4.2x10 ⁻³ ± 0.8x10 ⁻³	4.5x10 ⁻³ ± 1.2x10 ⁻³	14.1x10 ⁻³ ± 1.2x10 ^{-3†, §}
ratio free testosterone / DHEA	1.0x10 ⁻³ ± 0.3x10 ⁻³	0.6x10 ⁻³ ± 0.2x10 ⁻³	3.8x10 ⁻³ ± 0.6x10 ^{-3‡, §}
serum 17β-estradiol (nmol / l)	0.23 ± 0.03	0.18 ± 0.01	0.19 ± 0.02
ratio 17β-estradiol / free testosterone	26.6 ± 6.4	37.4 ± 13.0	3.4 ± 0.6 ^{†, §}

†p<0.005, ‡p<0.001 versus patients without danazol. §p<0.005 versus healthy subjects.
Abbreviations: ASD, androstenedione; DHEA, dehydroepiandrosterone.

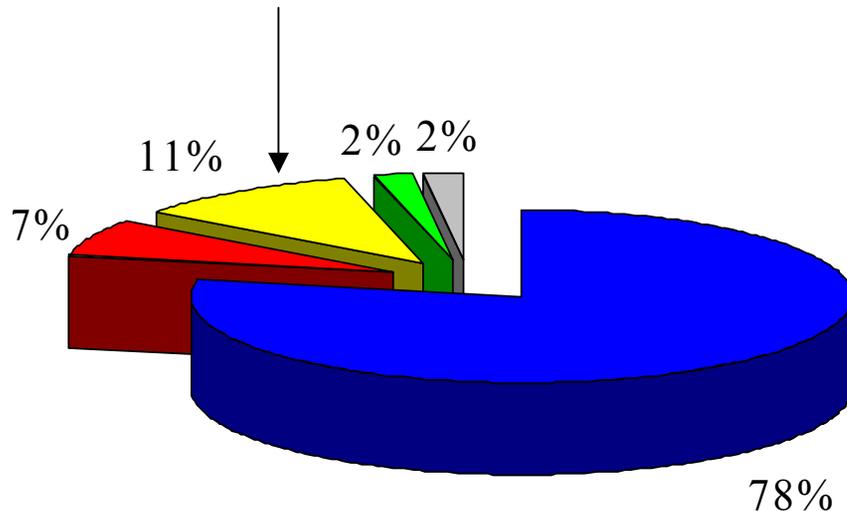
Conclusion

- This study demonstrated decreased ACTH in Type II HAE and decreased DHEA in patients with Type I and Type II HAE independent of danazol therapy; danazol amplify this effect.
- It also demonstrates that danazol induced a marked up-regulation of testosterone in relation to precursors and downstream 17β -estradiol.



Distribution of primary immunodeficiency diseases in the Czech Republic (Inhabitants: 10 100 000, patients: 577)

Complement deficiencies



- Antibody deficiencies (n = 450)
- Combined deficiencies (n = 39)
- Complement deficiencies (n = 66)
- Phagocytic disorders (n = 11)
- Other Primary Immunodeficiencies (n = 11)

Co-workers

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C1-inhibitor deficiency

Thank you for your attention.

