Adipocytokines in Graves' orbitopathy and the effect of high-dose corticosteroids

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Introduction

Background: Graves' Orbitopathy (GO) is a progressive eye condition associated with autoimmune thyroid disease, characterized by inflammation and swelling of soft orbital tissues - oculomotor muscles, connective tissue and adipose tissue. Adipose tissue produces adipokines, which are cytokine mediators and their roles in influencing endocrine processes are still being studied. Our aims were to identify relationships between serum levels of selected adipokines in patients with GO vs control group, and describe the effect of high-dose systemic corticosteroids (HDSC) on their levels.

Methods

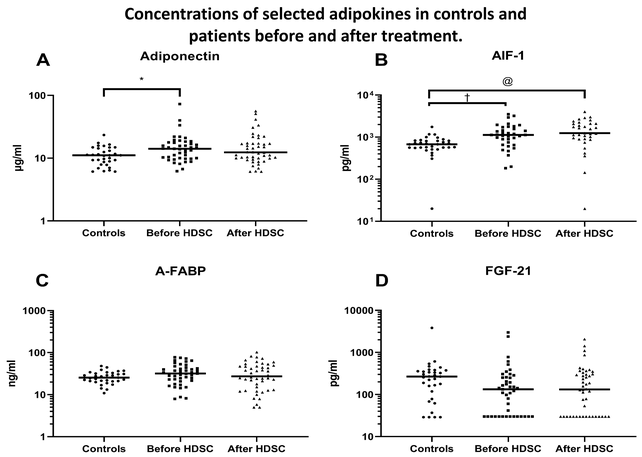
Data of 60 patients with with active GO (CAS ≥ 3) and received HDSC therapy were included in this study. Selected adipokines (adiponectin, allograft inflammatory factor 1 (AIF-1), A-FABP and FGF-21) were analysed using blood samples and compared against the control group (34 healthy volunteers without known thyroid dysfunction) [Diagram 1].

Our HDSC session consisted of 3 doses intravenous methylprednisolone (ivMP) and given for 3 days with bridging of prednisolone in between each session.

For comparative analysis blood samples were obtained and categorised into before HDSC sample and After HDSC sample [Table 1].

Blood samples obtained	
Blood samples	**Taken at**
Sample I/before HDSC group	Before initiation of HDSC
Sample II	Immediately after the third pulse of ivMP
Sample III	Outpatient visit 4–6 weeks after termination of the ivMP therapy
After HDSC group	Mean of Sample II and Sample III (if III not available - II was used)

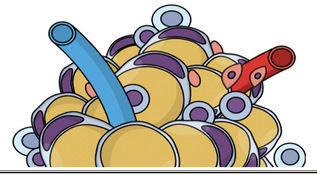
[Table 1 – above] **Blood samples categorised**



[Diagram 1 – on right] **Concentrations of selected adipokines in controls and patients before and after treatment.**
Panel A: adiponectin (µg / ml); Panel B: AIF-1 (pg / ml); Panel C: A-FABP (ng / ml) Panel D: FGF-21 (pg / ml). Concentrations on the Y axis are given in decimal logarithm. * p <0.05 and † p <0.001 for comparison of patients before treatment (Before HDSC) with the control group (Controls), @p <0.001 for comparison of patients after treatment (After HDSC) with the control group (Controls).

Results

Levels of adiponectin significantly differed among the three study groups (ANOVA p = 0.03), with the highest value in GO patients before initiation of HDSC, which was significantly higher than the control group (14.1 vs 11.1ug/ml; p = 0.03), but in the multivariate regression analysis, we did not find adiponectin as an independent marker of GO (Odds 1.089, p = 0.5). The adipokines multivariate analysis revealed however that the serum level of AIF-1 was significantly associated with the presence of GO after adjusting for clinical factors (age, sex, smoking and BMI) [Table 2].



Independent variables	Odds ratio (95% CI)	p-value
Age	**1.156 (1.067 - 1.291)**	**0.0024**
Sex (male)	0.196 (0.01288 - 1.571)	0.1781
Smoking	0.5502 (0.01983 - 9.570)	0.7008
BMI	0.8368 (0.6385 - 1.013)	0.1343
TSH	**0.544 (0.2898 - 0.9327)**	**0.0328**
Adiponectin	1.089 (0.9321 - 1.441)	0.4985
AIF-1	**1.003 (1.001 - 1.005)**	**0.0087**
A-FABP	1.013 (0.9404 - 1.101)	0.7503
FGF-21	0.9995 (0.9964 - 1.001)	0.7421

[Table 2]-**Multivariate analysis of variables associated with GO.** Bolded results shows clinical significance

Conclusion

Adiponectin levels have been reported in the past in patients with EO, but have never been shown to be an independent marker of EO. However, our multivariate analysis revealed a significant relationship between the presence / absence of EO and serum AIF-1 levels after adjusting for clinical parameters and TSH levels. Since AIF-1 is considered as a marker of macrophage activation (1), this finding could target EO treatment strategies to affect macrophages. Li et al suggested that the pathological intraorbital pressures encountered in GO could drive adipogenesis on its own, and potentially explain the clinical results suggesting that orbital decompression can reduce orbital inflammation (2,3). We conclude that the adipose tissue in the orbit affected by GO seems to be actively participating in the course of the disease and targeting its activation may lay the groundwork for the development of new therapeutic options.

References:

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(4) Images obtained from mindthegraph graphics

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