



**Karolinska
Institutet**

Inst. för Molekylär Medicin och Kirurgi

The HPA axis in type 2 diabetes

**Some aspects in relation to insulin sensitivity,
beta-cell function and IGF-I/IGFBP-1**

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Reabsalen, S2:01, Norrbacka,
Karolinska Universitetssjukhuset Solna

Fredagen den 14 mars 2014, kl. 09.00

av

Lisa Arnetz

Leg. läkare

Huvudhandledare:

Docent Michael Alvarsson
Inst. för Molekylär Medicin och Kirurgi
Karolinska Institutet

Fakultetsopponent:

Prof. Thomas Nyström
Inst. för Klinisk Forskning och Utbildning
Karolinska Institutet

Bihandledare:

Prof. Kerstin Brismar
Inst. för Molekylär Medicin och Kirurgi
Karolinska Institutet

Betygsnämnd:

Prof. Hans Arnqvist
Inst. för Klinisk och Experimentell Medicin
Linköpings Universitet

Dr. Neda Rajamand Ekberg
Inst. för Molekylär Medicin och Kirurgi
Karolinska Institutet

Prof. Jan Bolinder
Inst. för Medicin
Karolinska Institutet

Prof. Olle Kämpe
Inst. för Medicinska Vetenskaper
Uppsala Universitet

Stockholm 2014

ABSTRACT

Type 2 diabetes (T2D) is characterized by insulin resistance and β -cell failure, abdominal obesity, hypertension and dyslipidemia. These symptoms are also characteristic of states of hypercortisolism. The purpose of this thesis was to investigate how cortisol and regulation of the hypothalamus-pituitary-adrenal (HPA) axis is affected in subjects with T2D compared with healthy subjects (**study I**). We investigated the effects of improved insulin sensitivity and β -cell function during treatment with pioglitazone (**study II and III**) or sitagliptin (**study IV**), as well as effect of gender (**study I and III**), on serum cortisol and the HPA axis. We further examined the relationship between cortisol and insulin-like growth factor-I (IGF-I) and hepatic insulin sensitivity assessed using IGF-binding protein-1 (IGFBP-1).

Is adrenal sensitivity to ACTH affected by T2D or gender? (Study I)

Serum cortisol was measured basally, after stimulation of the HPA axis with 1 μ g adrenocorticotrophic hormone (ACTH) and feedback inhibition with 0.25 mg dexamethasone (DEX) in patients with T2D ($n = 21$, $HbA_{1c} = 49 \pm 2$ mmol/mol) and healthy controls ($n = 39$). Adrenal sensitivity to ACTH was higher in healthy women compared to men. This gender difference was lost in T2D, due to increased cortisol response in men. Neither basal serum cortisol nor sensitivity to DEX differed between subjects with T2D and controls.

Effect of pioglitazone on cortisol and IGF-I in T2D and IGT (Study II)

Overweight men ($BMI \geq 28$ kg/m²) with T2D ($n = 10$, $HbA_{1c} = 70 \pm 7$) and impaired glucose tolerance (IGT; $n = 10$) were treated with pioglitazone 30–45 mg daily for 12 weeks in addition to pre-existing therapy. Basal and stimulated cortisol did not differ at baseline. Improved insulin sensitivity and β -cell function after treatment was associated with decreased basal and peak cortisol after ACTH in T2D, while IGF-I increased. Paradoxically, basal and peak cortisol increased in IGT.

Are there gender differences in the effects of pioglitazone in T2D? (Study III)

Men ($n = 28$) and women ($n = 20$) with T2D and $HbA_{1c} > 57$ mmol/mol despite treatment with metformin and sulphonylurea were treated with pioglitazone 30–45 mg daily for 26 weeks. Basal cortisol increased in women despite improved insulin sensitivity. IGF-I and IGFBP-1 increased regardless of gender.

Is sitagliptin effect related to cortisol or hepatic insulin sensitivity? (Study IV)

Patients admitted to hospital for ACS and in whom an oral glucose tolerance test revealed previously unknown T2D ($n = 24$) or IGT ($n = 47$) were randomized to sitagliptin 100 mg once daily for 12 weeks, or placebo. Cortisol decreased regardless of treatment, but was unaffected by sitagliptin as was IGF-I and IGFBP-1.

Conclusions

Study I showed that adrenal sensitivity to ACTH is elevated in men with T2D, abolishing the gender difference seen in healthy subjects. This underscores the importance of accounting for gender in future studies on the HPA axis and T2D. In **study II and III**, improved insulin sensitivity and β -cell function by pioglitazone was associated with changes in basal and stimulated cortisol, but the effect differed between groups. IGF-I increased during pioglitazone therapy in patients with T2D. This may be an effect of improved lipid metabolism and contribute to improved insulin sensitivity. Cortisol levels decreased over the coming weeks after ACS, along with improved insulin sensitivity (**study IV**). The effect of sitagliptin did not appear to be exerted via lowering cortisol, or increasing hepatic insulin sensitivity as measured by IGFBP-1. Differences in findings between our studies may depend on heterogeneity of the groups, as e.g. metabolic control and obesity affect the HPA axis.