

ABSTRACT

Aim: The general aim of this thesis was to explore the associations between sex hormones and high blood pressure in men and women and to investigate their further role in the development of acute myocardial infarction particularly with regard to the large effect of type 2 diabetes, especially seen in women. Differences in levels of sex hormones and their specific effects in men and women might partially explain the differences in cardiovascular risk between men and women. Our specific aims were to investigate the relationship between sex hormones and high blood pressure as a major risk factor for cardiovascular disease, to investigate mechanisms that control the concentrations of sex hormone-binding globulin (SHBG), to investigate testosterone as a risk factor for AMI in men and women, to explore the modifying effect of type 2 diabetes on the outcome, and to investigate the association between sex hormones and cardiovascular disease, stroke and AMI, in men and women with or without type 2 diabetes.

Method: This thesis included studies on 2 cohorts: 1. A population survey in the municipalities of Vara and Skövde (VSC) 2002-2005 (n=2816, aged 30-74 years, 50% female, participation rate 76%); 2. A population survey in the municipality of Skara (SC3) 1993-1994 (n=1109, aged 40-80+ years, 50% female, participation rate 79%).

Results: Findings: Low concentrations of SHBG were associated with high blood pressure in men, whereas SHBG was independently associated with hypertension in postmenopausal women. We also found that insulin levels were independently associated with SHBG levels. Low testosterone levels in men with diabetes significantly predicted AMI independently of major cardiovascular risk factors. Endogenous estradiol concentrations were significantly associated with stroke risk in both sexes but with opposite relationships; estradiol was associated with reduced stroke risk in women, but with increased stroke risk in men.

Conclusion: In conclusion, concentrations of sex hormones predicted cardiovascular morbidity in both men and women, albeit differently. While testosterone was protective in men, estradiol and SHBG were protective in women. Moreover, SHBG seems to play an active role in the modulation of sex hormone effects, as it was found to be independently associated with hypertension. However, more studies are needed to explore the association of this globulin with diabetes and hypertension, in order to confirm our results suggesting a role of insulin in the control of SHBG. Correspondingly, the effects of estradiol in men seem negative while the effects of testosterone in women were uncertain. Thus, in each sex the characteristic hormone supports health. Diabetes also modified the association between concentrations of sex hormones and CVD in both sexes. These modifications might at least partially explain the loss of cardiovascular protection in women when they develop type 2 diabetes.

Keywords: testosterone, estradiol, sex-hormone binding globulin, sex, hypertension, type 2 diabetes, cardiovascular disease

ISBN: 978-91-628-8889-3

Sex hormones and cardiovascular risk in men and women

The Skaraborg Project

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid
Göteborgs universitet kommer att offentligen försvaras i hörsal 2119,
Hälsovetarbacke, Arvid Wallgrens Backe, hus 2, Göteborg,
fredagen den 14 februari 2014 kl 13.00

av

Bledar Daka

Fakultetsopponent:

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This thesis is based on the following papers, referred to in the text by their Roman numerals.

- I. Daka Bledar, Rosen Thord, Jansson Per Anders, Råstam Lennart, Larsson Charlotte A, Lindblad Ulf. Inverse association between serum insulin and sex hormone-binding globulin in a population survey in Sweden. *Endocr Connect* 2013;2(1):18-22.
- II. Daka Bledar, Rosen Thord, Jansson Per Anders, Larsson Charlotte A, Råstam Lennart, Lindblad Ulf. Low sex hormone-binding globulin is associated with hypertension: A cross-sectional study in a Swedish population. *BMC Cardiovasc Disord* 2013;13:30.
- III. B. Daka, R.D. Langer, C.A. Larsson, T. Rosen, P. Jansson, L. Råstam, U. Lindblad. Low concentrations of testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus. (Submitted).
- IV. B. Daka, U. Lindblad, V Dandolu, R.D. Langer. Concentrations of estradiol and testosterone predict cardiovascular morbidity in men and women. A prospective study in Sweden. Manuscript.