



# Progression in intima media thickness—the significance of hormonal biomarkers of chronic stress

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## KEYWORDS

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**Summary Objective:** The pathophysiological pathways from stress caused by psychosocial stress to IHD has not been dealt with very extensively. The objective of this study was to analyse the association between cortisol levels and progression in intima media thickness (IMT).

**Methods and results:** In 1998 and 2002, 95 participants went through a clinical investigation including ultrasound of the artery carotis communis. Progression in IMT was analysed in relation to levels of salivary cortisol in 1998 and the average levels of salivary cortisol in 1998/2002. Further, the significance of conventional coronary risk factors, testosterone and dehydro-epiandrosterone sulphate (DHEAS) were evaluated. Among the men, only age and HDL-cholesterol (negative) were significantly correlated with progression in IMT. Among the women, awakening cortisol response was significantly correlated with progression in IMT. Testosterone and DHEAS were borderline significantly associated (negatively) with progression in IMT in both genders.

**Conclusion:** Progression in atherosclerosis were determined by different risk factors in women and men. The awakening cortisol response was of great importance to IMT progression in women but not in men.

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## 1. Introduction

The introduction of the ultrasound technique has made it possible to estimate early, asymptomatic atherosclerosis by way of the intima media thickness (IMT). The association between IMT measured on the arteria carotis communis (ACC) and clinical

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ischemic heart disease (IHD) is well-established and the measure is often used in the field of cardiovascular epidemiology (Salonen and Salonen, 1993; Lynch et al., 1995; Crouse et al., 2002; O'Leary and Polak, 2002; Simon et al., 2002; Spence, 2002; Wikstrand et al., 2003).

A given IMT is an expression of the total effect of all the risk factors that a person has been exposed to until the time of examination. Progression in IMT is therefore a more precise estimate of the significance of a given risk factor than a given IMT in itself (Crouse, 2001). At the same time, it is important to be aware that the risk factors for progression in IMT do not necessarily include all those factors that increase the risk of acute myocardial infarct (AMI), insofar as some risk factors might only affect the atherosclerotic process, but not increase the risk of a rupture of the plaques and the development of AMI (Hegele, 1996; Spence and Hegele, 2004). Further, it has been shown that progression in IMT is associated with conventional risk factors (Sander et al., 2000; Lakka et al., 2001; Crouse et al., 2002; Chambless et al., 2002; Fujii et al., 2003) as well as with psychosocial risk factors (Everson et al., 1997a,b; Lynch et al., 1997a,b; Paterniti et al., 2001). Thus, a wide spectrum of risk factors has been shown to be associated with IHD and IMT as well as with progression in IMT.

However, the patho-physiological pathways from the psychosocial risk factors to IMT and IHD continue to be unclear. It is well known that acute, psychological stress increases cortisol secretion and that this leads to catabolism and mobilisation of energy. Further it is known that cortisol—via feedback mechanisms—impairs growth and reproduction (Sapolsky et al., 1986).

Because of the acute increase in cortisol secretion in connection with acute stress, chronic psychological stress has been expected to be associated with a chronic increase in cortisol. However, the findings in studies of chronic psychological stress and cortisol have not been consistent with this, insofar as studies have shown lower cortisol secretion in people with chronic psychological stress (Kristenson et al., 1998). Some researchers have suggested that low cortisol in people with psychological stress is due to exhaustion of the HPA-axis during long-term stress (a flat diurnal cortisol curve) (Bjorntorp and Rosmond, 2000; Bjorntorp et al., 2000). Changes in the cortisol receptor relationship may also have some influence (Sapolsky et al., 1986).

Only few studies have examined the connection between early atherosclerosis and cortisol. An early study in 1977 showed increased plasma cortisol in the

morning to be associated with the degree of coronary atherosclerosis in men, shown by way of angiography (Troxler et al., 1977). A recent cross-sectional study of 88 women and 42 men showed a negative association between increases in salivary cortisol in the morning and IMT in women, while no association could be shown in men (Eller et al., 2001).

The production of sex hormones is also affected by chronic stress (Sapolsky et al., 1986). There is a possibility that the level of these hormones could also influence the development of atherosclerosis. Studies have shown that testosterone is negatively associated with IMT in women, i.e. higher testosterone levels are associated with lower IMT, (Bernini et al., 1999; Golden et al., 2002) and men (De Pergola et al., 2003) as well as with progression of IMT in men (Muller et al., 2004).

This article describes a prospective study of conventional coronary risk factors, cortisol, testosterone and DHEAS, and progression in IMT over a four-year period. The objective of the study was to analyse the significance of hormonal biomarkers for stress, especially salivary cortisol, and conventional coronary risk factors on progression in IMT.

## 2. Materials and methods

### 2.1. Participants

In 1998, 130 participants were included in a prospective study of IMT, conventional risk factors (Eller and Netterstrom, 2001) and biomarkers of stress especially cortisol (Eller et al., 2001). All participants were in good health, had employment and volunteered in response to a public notification. A total of 95 participants (63 women and 32 men) agreed to be part of a follow-up study in 2002. The average follow-up time was 4.1 years. The study was approved by the local scientific ethical committee. All participants gave informed consent before the examination.

The participants were between 34 and 63 years old at the time of the follow-up study. The physiological characteristics of the participants are presented in Table 1. Those participants from 1998 who did not respond to the approach in 2002 (the non-participants) were significantly younger and had a better coronary risk profile than the participants. Further, the intima media thickness and salivary cortisol at awakening, i.e. the first awakening level of cortisol, among participants in 1998 was higher than among non participants, where as the change in salivary cortisol over the first 20 min after awakening in 1998 was lower among participants than among non participants.

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