C-REACTIVE PROTEIN IN RELATION TO THE DEVELOPMENT OF MICROALBUMINURIA IN TYPE 1 DIABETES: THE OXFORD REGIONAL PROSPECTIVE STUDY

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ABSTRACT

Objectives: To perform a longitudinal evaluation of high-sensitivity C-reactive protein (hs-CRP) in young people with type 1 diabetes (T1D) in relation to the development of microalbuminuria (MA).

Research Design and Methods: Hs-CRP was measured in 329 blood samples collected from 49 subjects with T1D with MA and 49 normoalbuminuric subjects matched for age, gender and duration of diabetes.

Results: In subjects developing MA a progressive rise in hs-CRP was detected with levels significantly higher in the years after the onset of MA when compared with levels before MA onset (p=0.003, age-adjusted p=0.06). After the onset of MA, hs-CRP levels were significantly higher in subjects with MA when compared with normoalbuminuric subjects (1.9[0.2-9.8] vs 1.1[0.2-6.4]mg/L; p=0.02; adjusted p=0.036).

Conclusions: In this population of young subjects with T1D, there was a significant increase in hs-CRP levels after the onset of MA, probably reflecting a general state of inflammation.
hs-CRP and microalbuminuria

C-reactive protein (CRP), a marker of inflammation (0), is increased in type 1 diabetes (T1D) (2-6), but its role in the development of diabetic nephropathy (DN) is not completely clear (4-7). In the present study we have performed a longitudinal evaluation of CRP in relation to the development of microalbuminuria (MA) in young people with T1D.

RESEARCH DESIGN AND METHODS

High-sensitive CRP (hs-CRP) was measured in 329 blood samples collected longitudinally from 49 (31 males) subjects with MA (MA+) (age mean±SD: 15.3±3.6 years; diabetes duration 5.6±2.8 years; age at diagnosis 9.5±4.1 years) and in 49 normoalbuminuric subjects (MA-), matched for age, gender and duration, from the Oxford Regional Prospective Study (ORPS), an incipient cohort study, established in 1986 to document the natural history of MA during childhood (8). The study was approved by regional ethics committees with written consent from the parents and assent from the children.

Annual assessment included measurements of height, weight and three consecutive early-morning urine samples for determination of the albumin-creatinine ratio (ACR). Annual blood samples were also collected for the central measurement of HbA1c and additional blood samples were stored. MA was defined as an ACR between 3.5-35 mg/mmol in males and 4.0-47 mg/mmol in females in two out of three consecutive early morning urine collections (8).

hs-CRP was measured in plasma samples by latex-enhanced nephelometry (N High sensitivity CPR assay) on a BN nephelometer (Dade Behring Inc, Milan, Italy). The lower limit of detection of this assay was 0.18 mg/L. hs-CRP levels higher than 10 mg/L were excluded from the analysis, as these are likely related to infections or other acute inflammatory processes (0,9).

Body mass index standard deviation scores (BMI SDS) were calculated from the UK growth reference charts (8). Statistical analyses were performed using SPSS 11.5. Data are expressed as mean±SD or median (range). Differences between groups were tested by independent t test. Analysis of covariance was used to assess trends in hsCRP. Associations between variables are expressed as regression coefficient (B)±SE.

RESULTS

Mean HbA1c levels were significantly higher in MA+ than in MA- subjects (10.9±2 vs 10.2±1.4%; p=0.03), whereas no differences were detected in demographic characteristics, BMI SDS, and insulin dose. In univariate analysis hs-CRP was significantly related to age (0.06±0.01/yr; p<0.001), duration of diabetes (0.06±0.01/yr; p<0.001), BMI SDS (0.26±0.07/SD; p<0.001) and logHbA1c (-0.93±0.40/1%; p=0.02) whereas there was a borderline relationship with insulin dose (0.28±0.14/U*Kg⁻¹, p=0.05). In a multivariate model the only factors independently related to hs-CRP were age (0.04±0.01/yr; p=0.008) and BMI SDS (0.17±0.08/SD; p=0.03). In a separate model including duration of diabetes instead of age, duration (0.04±0.01/yr; p=0.009) and again BMI SDS were the only factors independently related to hs-CRP.

Overall mean hs-CRP levels were not different between MA+ and MA- subjects (1.0[0.2-6.1] vs 0.9[0.2-4.0]mg/L). However, differences were detected when hs-CRP levels were analysed in relation to the time of MA onset. For this analysis, mean levels of hs-CRP before MA onset, at the time of MA onset and after the onset of MA were calculated for MA+ and, at corresponding years, for MA- subjects. A progressive rise in hs-CRP levels was observed in the MA+ group (p= 0.003) (figure 1), with significant higher levels after the onset of MA as compared with those before its onset (p=0.003; age-adjusted p=0.06). In contrast, no significant changes over time were
detected in the MA- group (p=0.3). After the onset of MA, hs-CRP levels were significantly higher in MA+ than in MA-subjects (1.9[0.2-9.8] vs 0.11[0.2-6.4]mg/dL; p=0.02). These differences persisted after adjusting for possible confounders, such as age, diabetes duration, BMI SDS and HbA1c (p=0.036).

CONCLUSIONS

The main finding of the present study was that, in young people with T1D, levels of hs-CRP were significantly raised after the development of MA. This is compatible with reported data showing that MA is associated with a state of sub-clinical inflammation and endothelial dysfunction (10). In subjects with T1D hs-CRP levels are increased when compared with healthy controls (2-6) and are related to signs of sub-clinical atherosclerosis (2) and to other markers of endothelial dysfunction (3-5). However, the role of CRP in relation to the development of DN is not clearly defined. Data from previous studies have raised the question whether CRP is the cause or the consequence of the vascular damage associated with MA (4,5,7). The results of the present study support the second option; inflammation being related to the MA onset rather than predicting risk for its development. A previous study conducted in adults with T2D has shown increased CRP levels associated with macroalbuminuria but not with MA. In other populations with T1D a significant difference in CRP levels was only detected between subjects with overt proteinuria and those with normoalbuminuria but not between microalbuminuric and normoalbuminuric subjects (4,6).

hs-CRP levels increased with age irrespective of MA status and this finding has been previously reported among children and adolescents (9). In our study this, together with the significant relationship between hs-CRP and diabetes duration, might indicate an effect of the chronic metabolic derangements of diabetes on CRP production. A positive relationship was found between BMI and hs-CRP levels consistent with previous data from large paediatric populations (12). A possible explanation for this relationship is that the hepatic production of CRP is regulated by IL-6 and TNF-alfa, two cytokines produced by adipose tissue (0). However, our observed association between the development of MA and hs-CRP was independent of BMI, suggesting the two are linked by a general state of inflammation.

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REFERENCES

FIGURE LEGEND

**Figure 1.** hs-CRP levels in relation to the development of microalbuminuria

Mean levels of hs-CRP were calculated for each specific time period (before the onset of MA, at the onset of MA and after MA onset MA) for each case (MA+) and each matched control (MA-).

Levels of hs-CRP significantly increased over time in the MA- group (p for trend =0.003) but not in the MA- group (p for trend =0.3). MA+ vs MA-: p= ns before and at the onset of MA; p= 0.03 after the onset of MA.