High-Sensitivity CRP Discriminates HNF1A-MODY From Other Subtypes of Diabetes

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OBJECTIVE—Maturity-onset diabetes of the young (MODY) as a result of mutations in hepatocyte nuclear factor 1-α (HNF1A) is often misdiagnosed as type 1 diabetes or type 2 diabetes. Recent work has shown that high-sensitivity C-reactive protein (hs-CRP) levels are lower in HNF1A-MODY than type 1 diabetes, type 2 diabetes, or glucokinase (GCK)-MODY. We aim to replicate these findings in larger numbers and other MODY subtypes.

RESEARCH DESIGN AND METHODS—hs-CRP levels were assessed in 750 patients (220 HNF1A, 245 GCK, 54 HNF4-α [HNF4A], 21 HNF1-β (HNF1B), 53 type 1 diabetes, and 157 type 2 diabetes).

RESULTS—hs-CRP was lower in HNF1A-MODY (median [IQR] 0.3 [0.1–0.6] mg/L) than type 2 diabetes (1.40 [0.60–3.45] mg/L; $P < 0.001$) and type 1 diabetes (1.10 [0.50–1.85] mg/L; $P < 0.001$), HNF4A-MODY (1.45 [0.46–2.88] mg/L; $P < 0.001$), GCK-MODY (0.60 [0.30–1.80] mg/L; $P < 0.001$), and HNF1B-MODY (0.60 [0.10–2.8] mg/L; $P = 0.07$). hs-CRP discriminated HNF1A-MODY from type 2 diabetes with hs-CRP <0.75 mg/L showing 79% sensitivity and 70% specificity (receiver operating characteristic area under the curve = 0.84).

CONCLUSIONS—hs-CRP levels are lower in HNF1A-MODY than other forms of diabetes and may be used as a biomarker to select patients for diagnostic HNF1A genetic testing.

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M aturity-onset diabetes of the young (MODY) is a rare monogenic form of diabetes and is often misdiagnosed as type 1 diabetes or type 2 diabetes (1,2). A correct genetic diagnosis of MODY is important for predicting the clinical course of disease, risk to relatives, and optimizing treatment. Therefore, cheap and novel biomarkers that help identify these patients are desirable.

The CRP gene has hepatocyte nuclear factor 1-α (HNF1A) binding sites in its promoter, and common variants in and around HNF1A are associated with circulating high-sensitivity C-reactive protein (hs-CRP) levels (3,4). Recently, Owen et al. (5) demonstrated that hs-CRP levels were reduced in 31 HNF1A-MODY patients compared with type 1 diabetes, type 2 diabetes, glucokinase (GCK) MODY, and normal control subjects, making it potentially a useful clinical test.

We aim to replicate this initial study in a larger cohort of patients and assess whether the reduction in hs-CRP is also seen in patients with mutations of other genes encoding hepatic nuclear factors (hepatocyte nuclear factor 4-α [HNF4A] and hepatocyte nuclear factor 4-β [HNF1B]).

RESEARCH DESIGN AND METHODS—Additional information about laboratory methods, study participants, and statistical analysis can be found in the Supplementary Data.

Study participants
hs-CRP level was assessed in plasma from 750 patients: 540 with a confirmed genetic diagnosis of MODY (220 HNF1A, 245 GCK, 54 HNF4A, and 21 HNF1B), 53 patients with type 1 diabetes, and 157 patients with type 2 diabetes.

RESULTS—Patient characteristics are presented in Supplementary Table 1. Subjects (29/750; 10.5%) had hs-CRP results >10 mg/L ($n = 16$ GCK-MODY, $n = 10$ type 2 diabetes, and $n = 3$ HNF4A-MODY) and were considered to have an acute inflammatory response and excluded from further analysis. This is in line with the protocol used by Owen et al. and previous studies of CRP (5,6).

HNF1A-MODY versus type 2 diabetes and type 1 diabetes
Plasma hs-CRP was significantly lower in HNF1A-MODY than type 1 diabetes and type 2 diabetes (median [IQR] 0.3 [0.1–0.6] mg/L versus 1.1 [0.5–1.85] mg/L [$P < 0.001$] and 1.4 [0.6–3.45] mg/L; $P < 0.001$), respectively (Fig. 1).

For discriminating HNF1A-MODY from type 2 diabetes, receiver operating characteristic (ROC) curve showed good discrimination (area under the curve [AUC] 0.84) and identified a cutoff hs-CRP of 0.75 mg/L with 79% sensitivity and 71% specificity (Supplementary Fig. 1). This equates to a positive predictive value (PPV) of 2.7% and a negative predictive value (NPV) of 99.7%, assuming a MODY prevalence of 1% (7). hs-CRP was less discriminative between HNF1A-MODY and type 1 diabetes with a ROC AUC of 0.78 (79% sensitivity and 67% specificity at a cutoff of <0.75 mg/L). This equates to a PPV of 2.4% and an NPV of 99.7%.
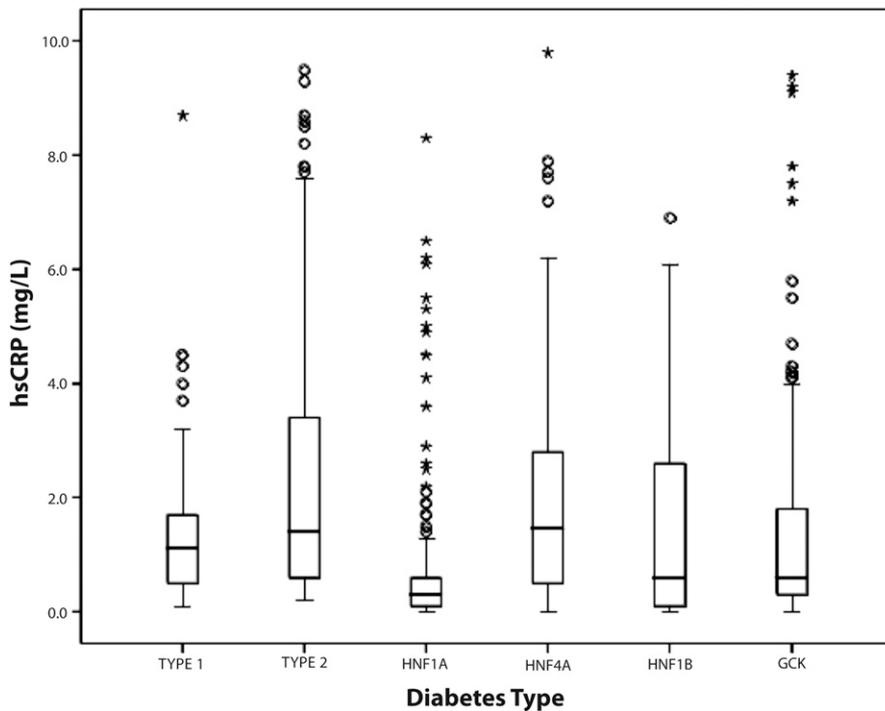
Figure 1—*Boxplot to show serum hs-CRP in type 1 diabetes* (n = 53), *type 2 diabetes* (n = 157), *HNF1A-MODY* (n = 220), *HNF4A-MODY* (n = 54), *HNF1B-MODY* (n = 21), and *GCK-MODY* (n = 245). *Box, median and IQR; whiskers, data range.* ○, *outliers* (>1.5× IQR); ★, *extreme values* (>3× IQR). *The data exclude all subjects with hs-CRP levels >10 mg/L.*

HNF1A-MODY versus other MODY subtypes

hs-CRP was lower in HNF1A-MODY (median [IQR] 0.3 [0.1–0.6]) than GCK-MODY (1.45 [0.46–2.88] mg/L; $P < 0.001$), HNF4A-MODY (0.6 [0.3–1.8] mg/L; $P < 0.001$), and HNF1B-MODY, although this did not reach statistical significance (0.6 [0.1–2.85] mg/L; $P = 0.07$).

To discriminate HNF1A-MODY from HNF4A-MODY, ROC curve analysis identified a cutoff hs-CRP <0.55 mg/L (AUC 0.76) achieving a sensitivity of 71% and a specificity of 70%. Discriminating HNF1A-MODY from all other MODY subtypes (HNF4A-, HNF1B-, GCK-MODY), a cutoff hs-CRP <0.55 mg/L (AUC 0.68) achieved 71% sensitivity and 55% specificity. This relationship persisted when discriminating HNF1A-MODY from all types of diabetes (71% sensitivity, 69% specificity).

Analysis of potential confounders can be found in the Supplementary Results.

CONCLUSIONS—We have confirmed in a large cohort of patients that plasma hs-CRP levels are lower in HNF1A-MODY than type 2 diabetes, type 1 diabetes, and GCK-MODY (5). We have shown for the first time that low hs-CRP levels are not seen in MODY because of mutations in other related transcription factors (*HNF4A, HNF1B*).

The best discrimination achieved with hs-CRP is between HNF1A-MODY and type 2 diabetes (79% sensitivity, 70% specificity). However, because MODY is rare (~1% of all diabetes [7]) compared with type 2 diabetes, this equates to a modest PPV of only 2.7%. Therefore, if hs-CRP was used as a marker for identifying HNF1A-MODY (hs-CRP <0.75 mg/L) in isolation the false-positive rate and number of unnecessary genetic testing would be high (37 to 1), suggesting that hs-CRP should be used in combination with other clinical characteristics. In contrast, a negative result (hs-CRP >0.75 mg/L), gives an NPV of 99.7% and therefore is good at ruling out HNF1A-MODY. Unlike type 1 diabetes where robust biomarkers, including pancreatic autoantibodies and persistent C-peptide production (1,8), already exist, few biomarkers currently distinguish type 2 diabetes from MODY.

hs-CRP was only reduced in HNF1A-MODY patients and not in the other genetic subtypes of MODY. This result may have been predicted since the hs-CRP gene has HNF1A binding sites in its promoter (9). This may prove to be useful as a tool to help prioritize the order of gene testing in patients with a high clinical suspicion of MODY. An hs-CRP level <0.55 mg/L should suggest *HNF1A* sequencing first, and levels >0.55 mg/L may warrant consideration of the other subtypes of MODY. This result may prove to be helpful as an adjunct to identify HNF4A-MODY patients, who are phenotypically similar to HNF1A-MODY.

An advantage of hs-CRP is that it is cheap and widely available. Current CRP assays, used to identify inflammation, measure down to levels of 0.2–0.3 mg/L and, therefore, a specific hs-CRP assay may not be necessary. It would be important to determine the comparability between routine CRP and hs-CRP assays before testing. A limitation of CRP is that it will be raised in inflammatory states, reducing its potential use as a discriminative tool. In addition, certain medications reduce CRP levels, such as statins (10), aspirin (11), and β-blockers (12), which are believed in some cases to reduce CRP by 20–30%. We did not have drug history available on individual patients, so we were unable to assess the impact of pharmacological agents on our results; however, Owen et al. (5) showed that removing subjects on statins and/or aspirin in their study did not alter their results.

In conclusion, we have confirmed that hs-CRP levels are lower in patients with HNF1A-MODY than other types of MODY, type 1 diabetes, and type 2 diabetes. hs-CRP is potentially a cheap, widely available biomarker that might aid in the cost-effective identification of patients with HNF1A-MODY.

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