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C-reactive protein and the risk of developing type 2 diabetes in Aboriginal Australians

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Abstract

Objective

To investigate the association between C-reactive protein (CRP) and the risk of developing diabetes in Aboriginal Australians.

Research design and methods

High sensitivity CRP levels were measured in 620 Aboriginal participants aged 20–74 years free from diabetes at baseline in a remote community in the Northern Territory of Australia. Participants were followed for a median of 11 years to identify newly diagnosed cases of diabetes. Cox proportional hazards models were used to assess the relationship of CRP levels with the risk of developing diabetes over the follow-up period.

Results

A total of 109 participants were newly diagnosed with diabetes. Incident rates were 10.8, 16.6 and 28.8 per 1000 person-years for people in the lower, middle and upper tertile groups of baseline CRP levels, respectively. After adjusting for age, sex, BMI, baseline glucose regulation status, total cholesterol, urine albumin to creatinine ratio, systolic blood pressure, smoking and alcohol drinking, the association between diabetes and CRP remained significant, with a hazard ratio of 1.23 (95% confidence interval (CI) 1.05, 1.45) corresponding to a doubling in CRP values. Similarly, the adjusted hazard ratio for development of diabetes in people in the upper tertile versus the bottom two tertiles of CRP was 1.75 (95% CI 1.19, 2.56).

Conclusions

CRP is independently associated with the development of diabetes in Aboriginal people. Our findings support a role of inflammation in the etiology of diabetes in the high risk population of Aboriginal Australians.

Keywords: inflammation; diabetes in minorities; incidence; Aboriginal health; epidemiology

There has been an increasing interest in the involvement of low grade inflammation in the pathogenesis of type 2 diabetes [1]. C-reactive protein (CRP) is an inflammatory marker produced and released by the liver under the stimulation of cytokines such as tumor necrosis factor-a and interleukins 1 and 6. It might affect the process of the atherothrombosis [2] and [3]. It has emerged as a powerful risk marker for cardiovascular disease [4], [5] and [6]. Inflammation has also been postulated to play a role in the pathogenesis of type 2 diabetes. Recent prospective studies have suggested that an elevated level of CRP is associated with an increased risk of developing type 2 diabetes [7], [8], [9] and [10]. Some of the risk may be mediated through obesity and factors related to insulin resistance [10].

Aboriginal Australians have a higher prevalence of diabetes than the general Australian population [11]. The causes of such a racial discrepancy in the prevalence of diabetes are still not clear. The distributions of CRP values vary significantly among race/ethnic groups [3] and [12]. The CRP level in Aboriginal population is much higher than that reported in other populations [13]. However, there is little information on inflammatory markers in high risk populations. There are no prospective cohort data from Aboriginal Australians evaluating the relationship between CRP and the development of type 2 diabetes. It is not known if inflammatory markers such as CRP can be useful for early detection of risk for diabetes in this high risk population. Therefore, we evaluated whether baseline CRP levels might independently predict future risk of diabetes among Aboriginal people, using prospective cohort data with a median of 11 years of follow-up.

1. Research design and methods

1.1. Study population

From 1992 to 1995, a community-wide chronic disease screening program was conducted in a remote island community in the Northern Territory of Australia [14]. The program surveyed 897 participants aged 20–74 years, representing 83% of the total 1082 eligible adults in the community. Among them, 136 participants had clinically manifested diabetes before the survey or were diagnosed with undetected diabetes at the baseline examination according to World Health Organisation (WHO) 1999 criteria based on fasting and 2 h post load plasma glucose levels [15]. Seven hundred and sixty one (761) participants free from diabetes at baseline were followed for up to 13 years with a median of 11 years. Serum samples were collected at baseline and stored at -70 °C until CRP testing. We further excluded 141 participants due to either insufficient quantity of the stored serum sample or no blood sample taken at baseline. The stored serum samples of 620 participants were retrieved for high sensitivity CRP testing in 2005. This project was approved by the Ethical Review Committee of the University of Queensland, the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services and Menzies School of Health Research and the community health board.

1.2. Ascertainment of diabetes

Development of diabetes during the follow-up period was determined through hospital and clinic records according to International Classification of Disease (ICD) codes: 250 in ICD-9 CM and E11 in ICD-10-AM. Only first diabetic incidents were included in the analysis. All participants were followed up to 30 April 2005. For those who were diagnosed as having diabetes during the follow-up period, their follow-up time was from the time of the initial screening visit when the serum sample was taken to the time of the first diagnosed diabetes. Those who had not reached an endpoint were considered “censored” on 30 April 2005. Participants who were free from diabetes and had died before the end of follow-up were censored at the time of death.

1.3. CRP measurements

All 620 baseline samples were analyzed for high sensitivity CRP using the immunoturbidimetric CRP assay on a Hitachi 917 analyzer (Roche Diagnostics Australia) with a detection limit of 0.03 mg/L. The assay's analytical range was from 0.1 to 20 mg/L. Samples with values greater than 20 mg/L were measured using diluted samples. The imprecision of the assay is less than 5%. The laboratory staff members who performed CRP analysis were not aware of the diabetes status of the study participants.

1.4. Measurements of baseline characteristics

During the baseline visit, a fasting venous blood sample was drawn for plasma glucose, serum total cholesterol and triglyceride measurements. For some participants who were free from diabetes at

baseline, plasma glucose levels were also measured 2 h after a 75 g oral glucose challenge. An individual with a fasting plasma glucose concentration of 5.6–

6.9 mmol/L was considered as having impaired fasting glucose (IFG) while those with a 2 h or random plasma glucose level of 7.8–11.0 mmol/L as impaired glucose tolerance (IGT). Impaired glucose regulation was defined as the presence of either IFG or IGT or both. Body weight, body height, waist circumference and blood pressures were measured at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Overweight was defined as BMI 25–29.9 kg/m^2 and obesity as BMI 30 kg/m^2 or greater. Self reported past and current cigarette smoking and alcohol drinking were recorded at baseline. All measurements of baseline characteristics had been obtained before incident diabetes was diagnosed.

1.5. Statistical analysis

Participants who were free from diabetes at baseline were divided into three groups according to age and sex specific CRP tertiles. We compared the baseline characteristics among the three groups using a Chi square test for dichotomous variables. To assess the association between CRP and the incidence of diagnosed diabetes, we calculated hazard ratios using Cox proportional hazards regression. We calculated crude hazard ratios and the hazard ratios stratified by each of BMI, waist circumference, impaired glucose regulation status and gender. To further assess the independent contribution of serum CRP at baseline to the risk of diabetes, hazard ratios and their 95% confidence intervals (CI) were estimated using the Cox proportional hazards model adjusting for potential confounding factors such as age, sex, an impaired glucose status, BMI, urine albumin to creatinine ratio and serum cholesterol. In addition to categorizing CRP into tertiles, we also used CRP as a continuous variable to examine the association between CRP and the risk of diabetes. Since the distribution of CRP values was highly skewed, the logarithmic transformed values were used. For the ease of interpretation of the hazard ratios, we used a base 2 logarithmic transformation. The hazard ratio of the transformed value was interpreted as the increase in diabetes risk corresponding to a doubling of the CRP values. All analyses were performed using Stata 9.0 [16].

2. Results

2.1. Baseline characteristics

The CRP values ranged from 0.1 to 220.2 mg/L. Table 1 shows the baseline characteristics of study participants in different baseline CRP tertiles. The three groups had similar distributions of age, sex, total cholesterol, high density lipoprotein cholesterol, blood pressures and alcohol drinking status. Those in the higher CRP tertile groups had higher BMI and waist circumference values and a higher prevalence of impaired glucose regulation. People in the middle tertile group were more likely to be smokers.

2.2. Development of diabetes and baseline CRP levels

During a total of 6010 person-years of follow-up, 109 study participants developed diabetes. The probability of developing diagnosed diabetes during the follow-up period for all study participants increased with the increasing CRP tertiles, as shown in Fig. 1. The same trend was observed among different BMI groups (Fig. 2). Table 2 shows the incidence rates of diagnosed diabetes according to baseline CRP levels. The incidence rate of diabetes increased with an increasing level of CRP. The crude incidence rates were 10.8, 16.6 and 28.5 per 1000 person-years for lower, middle and upper tertile groups, respectively. Stratified by each of body mass index, waist circumference, impaired glucose regulation and sex, the trend of an increased incidence of diabetes in the top tertile group remained in each stratum.

TABLE 1. Baseline characteristics of Aboriginal participants stratified according to baseline C-reactive protein (CRP) concentrations

	CRP tertile			***P*-value**
	Lower	**Middle**	**Upper**	
No. of participants	211	207	202	
Age (years)[a]	31.4 (11.8)	32.0 (11.3)	31.9 (11.3)	0.86
Body mass index (kg/m^2)[a]	21.1 (3.6)	23.3 (5.3)	24.3 (5.5)	<0.001
Waist circ. (cm)[a]	80.8 (10.3)	87.1 (13.2)	90.6 (14.2)	<0.001
Systolic pressure (mmHg)[a]	119.7 (18.7)	119.6 (16.9)	120.7 (18.0)	0.77
Diastolic pressure (mmHg)[a]	73.0 (12.8)	72.9 (14.0)	74.2 (13.0)	0.54
Total cholesterol (mmol/L)[a]	4.4 (0.9)	4.6 (1.2)	4.6 (1.1)	0.14
Triglycerides (mmol/L)[b]	1.65 (1.53, 1.79)	1.68 (1.55, 1.82)	1.76 (1.63, 1.90)	0.52
C-Reactive protein (mg/L)[b]	1.64 (1.49, 1.80)	4.83 (4.52, 5.15)	14.6 (13.3, 15.9)	<0.001
Male (%)[c]	113 (53.6)	109 (52.7)	108 (53.5)	0.98
Impaired glucose regulation (%)[c]	15 (7.1)	31 (15.0)	36 (17.8)	0.004
Smoking (%)[c]	155 (73.5)	165 (79.7)	134 (66.3)	0.01
Drinking (%)[c]	130 (61.6)	120 (58.0)	118 (58.4)	0.71

[a] Mean (standard deviation).
[b] Geometric mean (95% CI).
[c] Number (%).

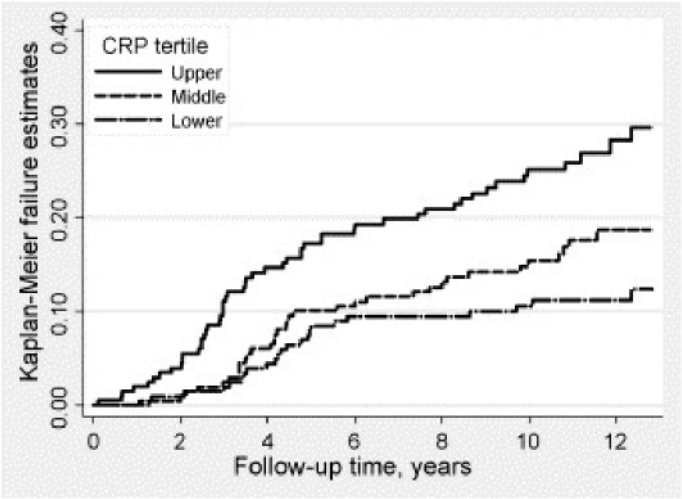

Fig. 1. Kaplan–Meier estimates of the cumulative distribution function for developing type 2 diabetes during the follow-up period in Aboriginal Australians.

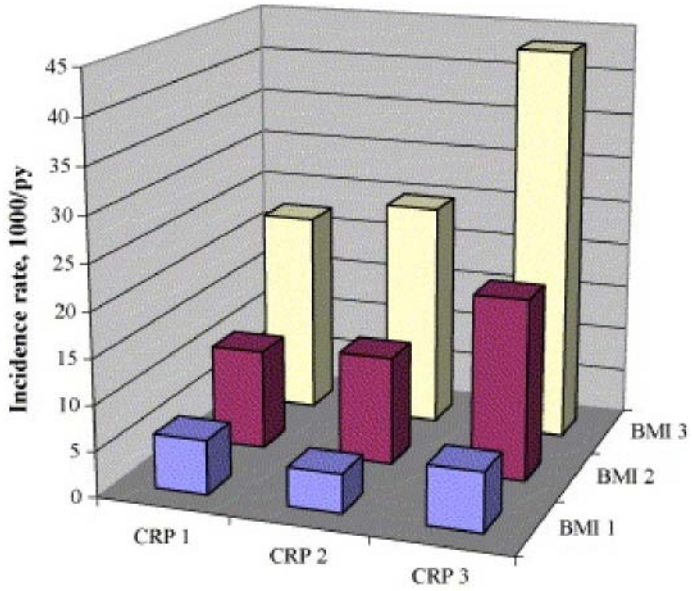

Fig. 2. Incidence rate of type 2 diabetes according to BMI and CRP tertiles.

TABLE 2. Incidence of diagnosed diabetes in Aboriginal people without diabetes at baseline according to baseline C-reactive protein (CRP) concentrations

Stratum	**CRP tertile**	**No. of diabetes cases**	**No. of person-years**	**Rate[b]**	**HR[a]**	**95% CI[a]**	***P*-value**
All participants	Lower	23	2135	10.8	1		
	Middle	34	2051	16.6	1.54	0.90, 2.61	
	Upper	52	1824	28.5	2.63	1.61, 4.30	<0.001
Stratified by BMI[a]							
BMI<25	Lower	18	1870	9.6	1		
	Middle	11	1344	8.2	0.85	0.40, 1.80	
	Upper	16	1187	13.5	1.39	0.71, 2.73	0.42
BMI 25+	Lower	5	265	18.9	1		
	Middle	23	707	32.5	1.68	0.64, 4.43	
	Upper	36	637	56.5	2.97	1.16, 7.57	0.014
Stratified by waist circumference							
(<80 cm, female;	Lower	10	1558	6.4	1		
<94 cm, male)	Middle	7	1181	5.9	0.93	0.35, 2.45	
	Upper	9	937	9.6	1.51	0.61, 3.71	0.57
(80+ cm,	Lower	13	578	22.5	1		

Stratum	**CRP tertile**	**No. of diabetes cases**	**No. of person-years**	**Rate[b]**	**HR[a]**	**95% CI[a]**	***P*-value**
female;							
90+ cm, male)	Middle	27	870	31.0	1.36	0.70, 2.64	
	Upper	43	887	48.5	2.14	1.15, 3.99	0.024
Stratified by glucose level							
Normal glucose	Lower	21	1982	10.6	1		
	Middle	20	1804	11.1	1.05	0.57, 1.94	
	Upper	34	1536	22.1	2.09	1.22, 3.61	0.01
IFT/IGT[a]	Lower	2	153	13.1	1		
	Middle	14	247	56.6	4.19	0.95, 18.45	
	Upper	18	288	62.5	4.65	1.08, 20.05	0.036
S							
Female	Lower	12	975	12.7	1		
	Middle	22	926	27.3	1.90	0.94, 3.85	
	Upper	36	784	43.0	3.69	1.92, 7.11	<0.001
Male	Lower	11	1161	9.2	1		
	Middle	12	1125	10.9	1.14	0.50, 2.57	
	Upper	16	1040	15.4	1.62	0.75, 3.50	0.43

[a] HR, hazard ratio; CI, confidence interval; BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
[b] per 1000 person-years.

The crude hazard ratios of diabetes were 1.54 (95% confidence interval: 0.90, 2.61) and 2.63 (95% CI: 1.61, 4.30), respectively, for middle and upper tertiles in comparison with the lowest tertile. Stratified by each of BMI, waist circumference, impaired glucose regulation and gender, the upper tertile consistently had a higher risk than the lower tertile even though it did not reach statistical significance in some strata (Table 2).

Table 3 shows the hazards ratio of diabetes adjusting for different sets of potential confounding factors in Cox proportional hazards models. After adjustment for age and sex, the CRP level as a continuous variable was significantly associated with the risk of diabetes. The hazard ratio for diabetes associated with a doubling of CRP value was 1.34 (95% CI: 1.17, 1.54). Further adjustment for BMI attenuated the observed hazard ratio to 1.24 (95% CI: 1.06, 1.44) but remained statistically significant. Adding variables such as baseline glucose level, total cholesterol, urine albumin to creatinine ratio, blood pressure, smoking and alcohol drinking did not alter the hazard ratio estimate (Table 3). No significant interactions between CRP and BMI, impaired glucose regulation and sex were observed.

TABLE 3. Adjusted hazard ratios of type 2 diabetes according to baseline CRP concentrations in Aboriginal Australians

	HR	**95% CI**	***P*-value (likelihood ratio test)**
CRP as continuous variable			
Adjusted 1[a]	1.34	1.17, 1.54	<0.001
Adjusted 2[b]	1.24	1.06, 1.44	0.006
Adjusted 3[c]	1.24	1.07, 1.45	0.005
Adjusted 4[d]	1.23	1.05, 1.45	0.01
CRP upper tertile versus the bottom two tertiles			
Adjusted 1[a]	2.11	1.45, 3.07	<0.001
Adjusted 2[b]	1.68	1.14, 2.46	0.008
Adjusted 3[c]	1.69	1.15, 2.47	0.007
Adjusted 4[d]	1.75	1.19, 2.56	0.004

[a] Adjusted for age, sex.
[b] Adjusted for age, sex and BMI.
[c] Adjusted for age, sex, BMI, and baseline glucose regulation status.
[d] Adjusted for age, sex, BMI, baseline glucose regulation status, urine albumin to creatinine ratio, total cholesterol, systolic blood pressure, smoking and alcohol drinking.

Due to relatively small numbers of diabetes cases in the lower and middle tertiles of CRP, we combined the two bottom tertile groups as the reference group to estimate adjusted hazard ratios for upper tertile. The hazard ratio adjusting for age and sex was 2.11 (95% CI: 1.45, 3.07). Similar to using CRP as a continuous variable, the hazard ratio was attenuated after adjusting for BMI. The hazard ratio adjusting for age, sex, BMI, impaired glucose regulation, total cholesterol, urine albumin to creatinine ratio, systolic blood pressure, smoking and alcohol drinking was 1.75 (95% CI: 1.19, 2.56).

One hundred and twenty eight participants developed cardiovascular disease or renal failure during the follow-up period. They are more likely to be diagnosed with diabetes in the follow up period than those without those conditions. Therefore, we recalculated adjusted hazards ratio excluding those who had cardiovascular disease or renal failure. Although the sample size was reduced substantially, the association between CRP and incident diabetes remained statistically significant for the doubling in CRP values, with a fully adjusted hazard ratio of 1.32 (95% CI: 1.08, 1.63). The adjusted hazard ratio for the upper tertile was 1.70 (95% CI: 0.99, 2.94).

3. Discussions

In this prospective cohort study in a high risk population of Aboriginal Australians, we observed a significant positive association between elevated CRP levels and incident diabetes. Higher CRP levels were strongly associated with BMI—an indicator of obesity, which is an important risk factor for the disease. Adjustment for BMI weakened the association between CRP and the risk of developing diabetes. However, the association remained statistically significant even after adjusting for age, sex, BMI, impaired glucose regulation, systolic blood pressure, total cholesterol, urine albumin to creatinine ratio, smoking and drinking. We found a 75% increased risk for those with upper tertile CRP values relative to the bottom two tertiles.

The association between inflammatory markers and incident diabetes has been examined in a few prospective studies in other populations [7], [8], [9], [10], [17], [18] and [19]. A study in Mexico City showed that the association was strong and significant in women but not in men [17]. An independent association was observed in women aged 45-year or older in the United States [7], in middle-aged men in Eastern Finland [10] and in Japanese American men and women [9]. In a matched case-control study in a high risk population of Pima Indians, no association between CRP and diabetes was found [20], possibly due to the lack of power due to the small sample size.

Adjusting for BMI and other factors attenuated, but did not eliminate, the association between CRP and incident diabetes in this study. This phenomenon has also been consistently documented in other populations [7], [8] and [10]. It was expected, due to the strong association between CRP and BMI and a strong association between BMI and risk of developing diabetes. Two possible explanations have been suggested. First, inflammation could be one mechanism by which known risk factors, such as obesity and factors related to insulin resistance, promote the development of diabetes [8]. Second, some of the risk of CRP could be mediated through those known risk factors [10].

Although the estimates of the hazards ratios varied among different strata, no significant interactions were observed. It should be noted that the small size in some strata might have hampered our ability to find significant interactions. Most previous prospective studies of Caucasian populations examined either men [8] and [10] or women alone [7]. Studies in Mexicans [17] and Japanese Americans [9] examined and compared the associations between CRP and incident diabetes in both sexes. In both studies the association tended to be higher in women than in men. Hak et al found a stronger association of inflammatory markers with insulin concentrations in elderly women than in men [21]. Aboriginal women with diabetes experienced a higher risk of coronary heart disease than Aboriginal men [22]. Whether CRP plays a more important role in females and in overweight and obese individuals in Aboriginal Australians remains to be further examined with large study samples.

The study population had a higher prevalence of diabetes than the general Australian population [11]. In addition, they also have higher CRP levels than other populations [13]. The strong and independent association between CRP and the risk of developing diabetes suggests that inflammation in may be partly responsible for the increased risk of diabetes in this population. Therefore, controlling inflammation may have important implications in prevention of diabetes and its complications in this population.

Our findings add to the growing body of evidence implicating low-grade inflammation as an independent predictor of diabetes. However, the exact effect of inflammation on glucose metabolism in humans is still unclear. There are several possible mechanisms through which inflammation might impair insulin action [23]. It has been postulated that type 2 diabetes may be a manifestation of activated innate immunity [1]. Inflammatory cytokines can attenuate insulin-induced suppression of hepatic glucose production, decrease lipoprotein lipase activity and stimulate lipolysis in adipose tissue [24]. Several drugs with anti-inflammatory properties lower both acute-phase reactants like CRP and glycemia [1] and [25]. The West of Scotland Coronary Prevention Study showed that pravastatin therapy resulted in a 30% reduction in the risk of developing type 2 diabetes. The anti-inflammatory effects of pravastatin might be partly accountable for the reduction [26].

This study has several strengths. Over 80% adults in the community were included in the cohort with a complete follow-up. The participants with both clinically diagnosed and survey diagnosed diabetes according to plasma glucose values at baseline were excluded. The baseline measurements of exposure CRP levels were determined by the laboratory persons who were not aware of the future diabetes status. The diagnosis of diabetes during the follow-up period was not influenced by the baseline CRP levels since the information was not available to the clinicians who made the diagnosis. However, a few limits of this study should be addressed. First, the onset of type 2 diabetes is usually insidious. The diabetes cases in this study were identified through hospital and clinical records, and some participants with diabetes might not have been identified. This could have biased our results toward the null. Second, misclassification of exposure cannot be excluded since only one blood sample was taken for each participant for CRP testing. Acute infections lead to temporarily increased CRP levels, which do not represent the true basal CRP value. Even the baseline CRP value measured when the participant was free from acute infections might still not represent the usual CRP level during the long-term follow-up period due to within-person variability. This bias, referred to as

regression dilution bias [27] and [28], could have also biased our effect estimates toward the null. Third, due to a relative small sample size, especially a small number of diabetes cases, we combined the two bottom tertile groups as the reference for calculating hazard ratios. Since the reference group might have contained individuals with an elevated CRP concentration as well as an increased risk of diabetes, the hazard ratios that were reported in this study represented conservative estimates of risk of CRP for diabetes. Fourth, some lifestyle factors were not included in this study. Guest and O'Dea reported that Aboriginal people consumed more salt and were more likely to eat takeaway food as a meal than non-Aboriginal Australians [29]. It is not clear to what degree the observed association reflects the effects of diet and lifestyle differences.

In conclusion, we show that a positive association between levels of CRP and incident diabetes, which supports a role of inflammation in the etiology of diabetes in the high risk population of Aboriginal Australians. The association was independent of established risk factor for diabetes. Therefore, inflammatory markers, like CRP, can be useful for early detection of high risk individuals.

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