Association Between Elevated Serum C-Reactive Protein and Triglyceride Levels in Young Subjects With Type 1 Diabetes

ANA M. LADEIA, MD, PHD[1]
ERIDAN STEFANELLI, MD[1]
CAROL LADEIA-FROTA, MD[1]
AGNALUCE MOREIRA, PHD[2]
ANGELA HILTNER, MD[3]
LUIS ADAN, MD, PHD[3,4]

Cardiovascular disease is the major cause of mortality and morbidity in individuals with diabetes (1,2). Increased plasma concentrations of acute-phase proteins have been reported in adult patients with either type 2 (3,4) or type 1 (5,6) diabetes. However, there have been few studies to determine plasma high-sensitivity C-reactive protein (hs-CRP) levels in young diabetic patients (7,8). This study evaluated the levels of hs-CRP and their correlation with metabolic profile in very young patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This sectional study included 45 consecutive young patients (26 boys) who fulfilled the inclusion criteria (diagnosed as type 1 diabetic, followed up at a public health assistance center, serum creatinine level <1.3 mg/dl, and normal thyroid-stimulating hormone values) and 30 healthy subjects (12 boys) matched by age (±3 years) and BMI. Exclusion criteria were hypertension, overweight or obesity, smoking, any infection having been diagnosed during the previous 3 months, and treatment for inflammatory or chronic infectious disease.

Measurements of pulse rate, blood pressure, height and weight, and specific clinical examination of throat, eyes, nose, ears, skin, and feet were performed. Laboratory data included fasting blood glucose, HbA_{1c} (A1C), total cholesterol, HDL and LDL cholesterol, triglycerides, serum creatinine, thyroid-stimulating hormone, and hs-CRP. Hs-CRP was determined by nephelometry.

Differences in the means were evaluated by the Student's *t* test. The hs-CRP data were analyzed by the Mann-Whitney nonparametric test. Spearman's correlation test was used when indicated. A *P* value <0.05 defined statistical significance.

RESULTS

The mean ages were 14.1 ± 4.6 years (95% CI 3–23) for the type 1 diabetic patients and 14.6 ± 3.9 years (6–22) for healthy subjects ($P = 0.6$). BMI was similar in the two groups (19.1 ± 2.6 vs. 19.6 ± 0.8 kg/m^2, $P = 0.4$). No differences were observed for systolic or diastolic blood pressure (106.3 ± 14.0 vs. 103.3 ± 11.3 mmHg, $P = 0.3$, and 66.6 ± 7.5 vs. 65.6 ± 7.6 mmHg, $P = 0.4$, respectively). Total cholesterol values were higher in diabetic patients than control subjects (173.7 ± 40.6 vs. 148.8 ± 32.6 mg/dl, $P = 0.006$); the other lipid variables were similar in the two groups. In the type 1 diabetic patients, age at diagnosis was 8.9 ± 4.9 years (0.5–18), and the duration of disease was 5.6 ± 4.1 years (0.9–17). Mean fasting blood glucose was 217.2 ± 127.7 mg/dl, and A1C was 10.2 ± 2.7%. None of the type 1 diabetic children were taking regular medications other than daily insulin. Microalbuminuria was positive in 10 of 35 patients (28.6%).

Type 1 diabetic patients had higher mean (1.7 ± 2.2 vs. 1.0 ± 1.6 mg/l, $P = 0.012$) and median (0.67 vs. 0.28 mg/l, $P = 0.016$) serum concentrations of hs-CRP than control subjects. In the diabetic patients, hs-CRP levels were positively correlated with triglycerides ($r = 0.32$, $P = 0.03$) and with the triglyceride-to-HDL ratio ($r = 0.33$, $P = 0.03$) (Fig. 1) but not with glycemic control, other lipid variables, or microalbuminuria. A positive correlation was also observed between hs-CRP and disease duration ($r = 0.32$, $P = 0.028$).

CONCLUSIONS

The present study compared young type 1 diabetic patients with nondiabetic control subjects, and it was shown that hs-CRP was higher in this diabetic population. In adult patients, hs-CRP did not show any significant difference between the diabetic and control subjects (9). In another study, type 1 diabetic patients had significantly higher hs-CRP levels than nondiabetic individuals, and this was correlated with the intima-media thickness of the carotid artery (7). It is interesting to note that in the present study, the diabetic group was younger than the groups in other studies (7,9,10) and had shorter disease duration. Furthermore, the positive correlation between hs-CRP levels and diabetes duration strongly suggests that information on inflammatory state, even in young diabetic patients with short disease duration, can be of clinical relevance because atherosclerosis and vascular damage begins in childhood (11).

In accordance with others (10), the present study demonstrated that hs-CRP levels were positively correlated with triglycerides and triglyceride-to-HDL ratio but not with the other lipid variables. These results are consistent with data in nondiabetic subjects (12,13) and in type 2 diabetic patients (14). The association between triglyceride-to-HDL ratio and hs-CRP level suggests that this unfavorable lipid profile may facilitate the formation of foam cells in the arterial wall, increasing the inflammatory activity in young type 1 diabetic subjects. Despite their size, triglyceride-rich remnants of VLDL and chylomicron metabolism are capable of penetrating the artery wall and

From the [1]Bahian Medical and Public Health School and Post-Graduate of Bahian Medical and Public Health School, Science Development Foundation of Bahia, Bahia, Brazil; the [2]LPC Clinical Pathology Laboratory, Bahia, Brazil; the [3]Pediatric Unit, State of Bahia Center for Diabetes and Endocrinology (CEDEBA), Bahia, Brazil; and the [4]Department of Pediatrics, Federal University of Bahia School of Medicine, Bahia, Brazil.

Address correspondence and reprint requests to A.M. Ladeia, Rua Altino S de Barros 241 s506 Itaigara, Salvador-BA, Brazil, CEP 41 810 570. E-mail: analadeia@uol.com.br.

Received for publication 22 October 2005 and accepted 26 October 2005.

Abbreviations: CRP, C-reactive protein; hs-CRP, high-sensitivity CRP.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

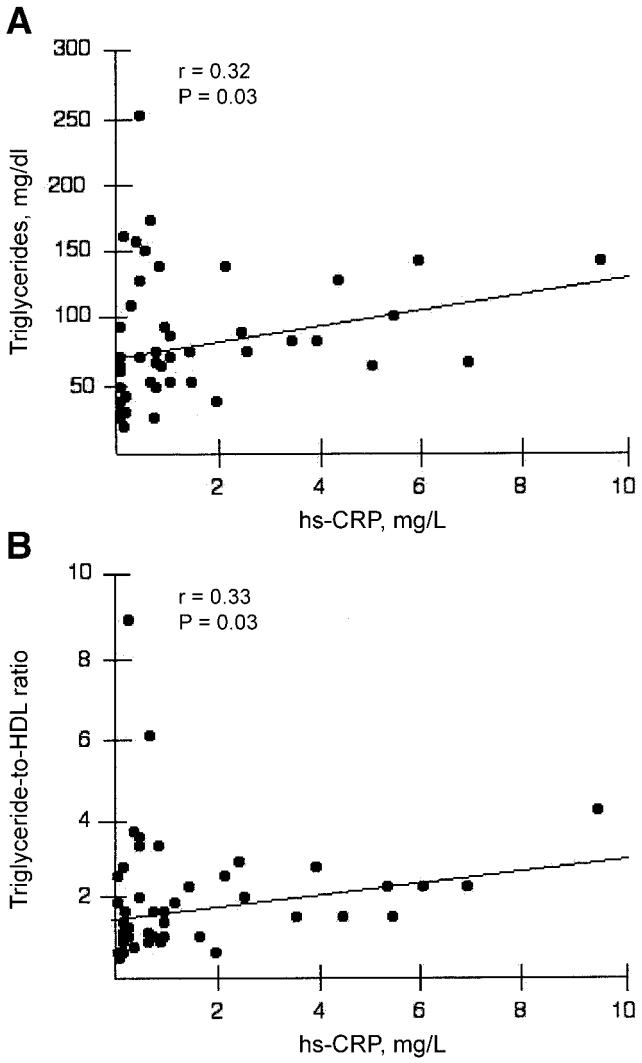

Figure 1—*Correlation between triglycerides and hs-CRP levels (*A*) and triglyceride-to-HDL ratio and hs-CRP levels (*B*) in type 1 diabetic patients.*

the subintimal space, where they are ingested by macrophages and become proatherogenic foam cells (15). As the mass of circulating triglyceride rises, the average LDL and particle size is reduced (16), and these LDL particles would appear to be more susceptible to oxidation, a process that increases their atherogenicity. Available evidence also indicates that as triglyceride levels rise, the clearance rates of the major HDL proteins apoAI and apoAII are enhanced (17). This results in the generation of smaller and denser HDL, which is less capable of participating in the process of reverse cholesterol transport and is consequently less protective (18,19). Despite these plausible biological explanations, the association between lipid variables and CRP is not completely established, even in adult patients (20).

As in other studies (21), we found no correlation between hs-CRP and glycemic control. In addition, a recent study (22) failed to show a decrease in hs-CRP levels after intensive glycemic control in type 1 diabetic patients; in contrast, it showed increased concentrations of hs-CRP and tumor necrosis factor receptor 1 among those who gained weight. Indeed, the expression of hs-CRP as a marker of inflammatory activity is very complex and cannot only be explained by the hyperglycemic condition (10).

Somewhat unexpectedly, hs-CRP was not associated with microalbuminuria, an early marker of endothelial dysfunction, even in type 1 diabetes of short duration (23). The low frequency of individuals with positive microalbuminuria in this study and the skewed distribution of hs-CRP may explain this finding.

In conclusion, the present study has shown that hs-CRP levels are increased in very young type 1 diabetic patients, even with a relatively short disease duration. Plasma hs-CRP was correlated with triglycerides and triglyceride-to-HDL ratio, suggesting that strategies to decrease inflammatory activity should focus on the lipid profile as well. Moreover, the association of this inflammatory marker with lipid variables indicates an important linkage between type 1 diabetes and the risk of developing atherosclerosis.

Acknowledgments— E.S. was supported by the Research Foundation of Bahia (FAPESB), Bahia, Brazil.

References

1. Garcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and mortality in diabetics in the Framingham population: sixteen year follow-up study. *Diabetes* 23: 105–111, 1974
2. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H: The British Diabetic Association Cohort Study II: cause specific mortality in patients with insulin-treated diabetes. *Diabet Med* 16:466–471, 1999
3. Pickup JC, Mattock MB, Chusney GD, Burt D: NIDDM as a disease of innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 40:1286–1292, 1997
4. Pradhan AD, Manson MB, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
5. Shalkwijk GG, Poland DC, van Dijk W, Kok A, Emeis JJ, Drager AM, Doni A, van Hinsbergh VW, Stehouwer CD: Plasma concentration of C-reactive protein is increased in type 1 diabetic patients without clinical macroangiopathy and correlates with markers of endothelial dysfunction: evidence for chronic inflammation. *Diabetologia* 42:351–357,1999
6. Kilpatrick ES, Keevil BG, Jagger C, Spooner RJ, Small M: Determinants of raised C-reactive protein concentration in type 1 diabetes. *Q J Med* 93:231–236, 2000
7. Hayaishi-Okano R, Yamasaki Y, Katakami N, Gorogawa SI, Kuroda A, Matsuhisa M, Kosugi K, Nishikawa N, Kajimoto Y, Hori M: Elevated C-reactive protein associated with early-stage carotid atherosclerosis in young subjects with type 1 diabetes. *Diabetes Care* 25:1432–1438, 2002
8. Piccirilo LJ, Gonçalves M de F, Clemente EL, Gomes M de B: Markers of inflamma-

tion in type 1 diabetic patients. *Arq Bras Endocrinol Metab* 48:253–260, 2004
9. Basu S, Larsson A, Vessby J, Vessby B, Berne C: Type 1 diabetes is associated with increased cyclooxygenase- and cytokine-mediated inflammation. *Diabetes Care* 28:1371–1375, 2005
10. Schram MT, Chaturvedi N, Schalkwijk C, Ebeling P, Fuller JH, Stehouwer CD: Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetes Care* 26:2165–2173, 2003
11. Jarvisalo MJ, Harmoinen A, Hakanen M, Paakkunainen U, Viikari J, Hartiala J, Lehtimaki T, Simell O, Raitakari O: Elevated serum C-reactive protein levels and early changes in healthy children. *Arterioscler Thromb Vasc Biol* 22:1323–1328, 2002
12. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Ausgburg Cohort study, 1984 to 1999. *Circulation* 99:237–242, 1999
13. Onat A, Sansoy V, Yildirin B, Keles I, Uysal O, Hergenc G: C-reactive protein and coronary heart disease in western Turkey. *Am J Cardiol* 88:601–607, 2001
14. Francisco G, Hernández C, Chacan P, Mesa J, Sima R: Factors influencing CRP levels in the diabetic population. *Med Clin (Barc)* 124:336–337, 2005
15. Zilversmit DB: Atherogenesis: a postprandial phenomenon. *Circulation* 60:473–485, 1979
16. Shepherd J: Does size matter? LDL subfraction and coronary risk. *Br J Cardiol* 2:163–166, 1995
17. Brinton EA, Eisenberg S, Breslaw JL: Increased apoAI and AII fractional catabolic rate in patients with low HDL cholesterol with or without hypertriglyceridemia. *J Clin Invest* 87:536–544, 1991
18. Barter P, Rye KA: High density lipoproteins and coronary heart disease. *Atherosclerosis* 121:1–12, 1996
19. Das DK: Cardioprotection with HDL. *Circulation Res* 92:258–260, 2003
20. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflamation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
21. Coulon J, Willems D, Dorchy H: Increase in C-reactive protein plasma levels during diabetes in infants and young adults. *Presse Med* 34:89–93, 2005
22. Schaumberg DA, Glynn RJ, Jenkins AJ, Lyons TJ, Rifai N, Manson JE, Ridker PM, Nathan DM: Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the Diabetes Control and Complications Trial. *Circulation* 111:2446–2453, 2005
23. Ladeia AM, Ladeia-Frota C, Pinho L, Stefanelli E, Adan L: Endothelial dysfunction is correlated with microalbuminuria in children with short-duration type 1 diabetes. *Diabetes Care* 28:2048–2050, 2005