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Effect of Metformin and Sulfonylurea on C-Reactive Protein Level in Well-Controlled Type 2 Diabetics with Metabolic Syndrome

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The objective of this study was to examine the effect of the antihyperglycemic agents metformin (insulin sensitizer) and glibenclamide (insulin secretory agent) on the serum level of C-reactive protein (CRP) in well-controlled type 2 diabetics with metabolic syndrome. The participants were diabetic patients being followed in the medical outpatient clinic of King Abdulaziz University Hospital. The inclusion criteria were type 2 diabetics with the metabolic syndrome, well-controlled blood glucose on metformin alone or glibenclamide alone, and exclusion of major medical illness. Patients were divided into two groups according to the antihyperglycemic agent used. CRP level was measured 4-wk apart and the mean was calculated. The following data were collected from the study groups: age, sex, body mass index (BMI), duration of diabetes, smoking history, presence of hypertension, hyperlipidemia, and mean CRP level. A total of 110 patients were studied, 65 using metformin and 45 using glibenclamide. CRP level was significantly lower in patients using metformin for blood glucose control compared with those using glibenclamide, 5.56 and 8.3 mg/L, respectively ($p = 0.01$). A significantly higher level was observed in hypertensive and hyperlipidemic patients compared with normotensive and normolipidemic, 5.3 vs 3.2 mg/L and 7.1 vs 4.3 mg/L, respectively ($p = 0.02, 0.01$). There was a statistically significant correlation between CRP and BMI ($r = 0.37$) and age ($r = 0.36$) (all $p = 0.01$). The data showed that metformin decreases the level of circulating CRP, a marker of inflammation, more than glibenclamide.

Key Words: C-reactive protein; metformin; type 2 diabetics.

Introduction

Diabetic individuals have a two- to fivefold increased risk of developing angina, myocardial infarction, and congestive heart failure *(1)*. A predominant complication of type 2 diabetes is accelerated development of atherosclerosis. Traditional risk factors, including hypertension, elevated plasma triglyceride, and low high-density lipoprotein (HDL) cholesterol level, only partly explain the excess risk of developing atherosclerosis in type 2 diabetics *(2,3)*. It has become increasingly evident that atherosclerosis is a very complex event with multiple etiologies and mechanisms. There is increasing appreciation of less widely recognized (nontraditional) risk factors, including C-reactive protein (CRP); plasma activator inhibitor-1; fibrinogen; and small, dense low-density lipoprotein (LDL), that may contribute to these events or at least reflect the activity of these processes. It has been recognized that type 2 diabetes is associated with increased prevalence of several traditional risk factors, which may result, in part, because of insulin resistance *(2,4,5)*. It is now apparent also that many nontraditional risk factors may be part of the insulin resistance syndrome (metabolic syndrome) *(6–10)*. There is clear evidence that metabolic syndrome is associated with greatly increased risk of coronary heart disease (CHD) *(11,12)*. It would seem logical that reduction of these risk factors (traditional and nontraditional) may result in inhibition of atherosclerosis and reduction of CHD risk in diabetics. It remains unclear whether lowering glucose, a fundamental component of diabetic therapy, is an effective method to reduce the incidence or progression of CHD in type 2 diabetics *(13,14)*.

It is becoming increasingly important to study the effect of diabetic medications on the levels of traditional and nontraditional risk factors. In 2002, a study conducted by Chu et al. *(15)* suggested that both metformin and troglitazon have beneficial effects on several traditional and nontraditional cardiovascular risk factors. Several studies have demonstrated that the thiazolidinedione class of medication can have a favorable effect on coagulation/fibrinolysis factors, LDL particle size, and CRP *(16,17)*. A recent study by Minamikawa et al. *(18)* showed that troglitazon successfully reduces carotid arterial wall thickness in patients with

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Table 1
Distribution of Variables
in Patients Using Metformin and Glibenclamide[a]

	Group 1 (n = 65)	Group 2 (n = 45)	P value
Age (yr) (mean ± SD)	51 ± 6	52.4 ± 9	0.3
Sex (F:M)	43:22 (2:1)	28:17 (1.6:1)	0.5
Duration of diabetes (yr) (mean ± SD)	4.5 ± 2.9	5 ± 2.2	0.4
BMI (kg/m^2) (mean ± SD)	29 ± 3.8	30.8 ± 6.3	0.3
CRP (mg/L) (mean ± SD)	5.56 ± 1.5	8.3 ± 1.4	0.01
Hypertension (n [%])	24 (37)	18 (40)	0.3
Hyperlipidemia (n [%])	30 (46)	21 (48)	0.4
Smoking (n [%])	25 (38)	18 (40)	0.6

[a]Group 1 = diabetics using metformin; Group 2 = diabetics using glibenclamide.

type 2 diabetes. In a randomized crossover study by Yudkin et al. *(19)*, 16 wk of treatment with insulin resulted in reduction of CRP level.

Sulfonylurea and biguanide metformin are the oldest and most commonly used class of oral hypoglycemic drugs *(20, 21)*. The aim of the present work was to compare the effect of these two antidiabetic medications with different mechanisms of action, metformin (insulin sensitizing agent) and glibenclamide (insulin secretory agent), on CRP level (one of the nontraditional risk factors) in patients with type 2 diabetes and metabolic syndrome. Patients with metabolic syndrome were chosen to ensure the presence of insulin resistance and a high level of CRP. To ensure that differences in the level of CRP resulting from these therapies were not a consequence of dissimilar glycemic control, the study was conducted on subjects with reasonably well-controlled blood glucose.

Results

A total of 110 patients fulfilled the inclusion criteria. Sixty-five were taking metformin (group 1) and 45 taking glibenclamide (group 2). The duration of use was 3.5 ± 2.1 yr for metformin and 4.2 ± 2.3 yr for glibenclamide. As shown in Table 1, mean CRP was significantly lower in patients using metformin for blood glucose control compared with those using glibenclamide. There was a statistically significant positive correlation (p = 0.01) between CRP level and BMI (r = 0.37) and also between CRP level and age (r = 0.36). Mean CRP was significantly higher in hypertensive compared with normotensive patients, 5.3 ± 1 vs 3.2 ± 1.2 mg/L (p = 0.02) and in hyperlipidemic compared with normolipidemic patients, 7.1 ± 0.3 vs 4.3 ± 1.2 mg/L (p = 0.01). A statistically significant sex difference was observed in the mean CRP level, being higher in females compared with males: 7.1 ± 1.5 vs 4.9 ± 1.1 mg/L (p = 0.002).

Discussion

The present study has shown that patients taking metformin have a lower CRP level compared with those taking glibenclamide. CRP is an acute-phase protein produced in response to a wide range of stimuli including infection, inflammation, and injury *(22)*. It has previously been shown that CRP is higher in patients with diabetes or glucose intolerance than in control subjects *(23)*. In a study conducted by Pickup et al. *(24)*, CRP was higher in 19 patients with noninsulin-dependent diabetes (NIDD) and syndrome-X than in patients with NIDD without syndrome-X. Clustering of cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and glucose intolerance had been given several names including syndrome-X, metabolic syndrome, the deadly quarter, and insulin resistance syndrome *(25,26)*. According to the World Health Organization (WHO) definition of the metabolic syndrome (MS) proposed in 1998 *(27)*, insulin resistance as measured by the homeostasis model assessment (HOMA) was not included as a component of the syndrome because insulin resistance is seen in ~90% of patients with type 2 diabetes and the prevalence of the MS did not change much when insulin resistance was included as a component *(28)*.

The present study showed a strong positive correlation between CRP level and BMI, hypertension, and dyslipidemia. The Cardiovascular Health Study *(29)* showed a significant positive correlation between CRP and BMI, triglyceride (TG), and uric acid and a negative correlation with HDL cholesterol. Haverkate et al. *(30)* and others *(31–33)* have also shown that CRP level increased significantly with BMI and blood pressure.

There is clear evidence that increased CRP is an independent risk factor for CHD *(30,31,34,35)*. This might be explained by its proatherogenic and prothrombotic action *(36)*, its capacity to stimulate tissue factor production by macrophage *(37)*, and its interaction with LDL *(38)*. Interestingly, we observed a higher level of CRP in females compared with males, which was also observed by Frohlich et al. *(32)*. This may explain the high risk of CHD in female diabetics noticed in other studies *(39–43)*. A strong correlation was also observed between CRP and age, which is in agreement with others finding *(44)*. Both groups in the present study had fairly controlled blood glucose, which suggests that the different effects on CRP level detected between metformin and glibenclamide are not related to a difference in glucose control.

Metformin is an insulin-sensitizing agent. It increases insulin-mediated glucose disposal and decreases hepatic glucose output. As noted earlier, many cardiovascular risk factors (traditional and nontraditional) are modulated by insulin resistance and are frequently elevated in insulin resistance

syndrome *(4,15,45–47)*. Agents that substantially improve insulin resistance such as metformin may therefore prove more useful in reducing levels of these factors. In the UK Prospective Diabetes Study, it was shown that metformin used as monotherapy in obese subjects was associated with a significant decrease in diabetes-related deaths and all-cause mortality by 42 and 36%, respectively *(48)*. The current study showed that metformin seemed to have a greater effect on CRP level than did glibenclamide. The difference between diabetic agents may have important implications in the progression of atherosclerosis and development of cardiovascular events. Further long-term studies are needed on this important issue.

Materials and Methods

Subjects

King Abdulaziz University Hospital is a teaching hospital in Jeddah, the western province of Saudi Arabia. Diabetic patients being followed in the medical outpatient clinic were studied. Those who fulfilled the following criteria were selected:

1. Type 2 diabetics with the MS—defined according to the WHO criteria *(22)* as a person with type 2 diabetes who fulfills two of the following criteria: hypertension (if the patient is known to have hypertension or his or her blood pressure is >160 mmHg systolic and >90 mmHg diastolic), dyslipidemia (elevated TG >1.7 mmol/L and/or low HDL: <0.9 mmol/L in men and <1.0 mmol/L in women), obesity (BMI > 30 kg/m^2 and/or high waist hip ratio of >0.9 in men and >0.85 in women), and microalbuminuria [urinary albumin excretion ratio (AER) >20 μg/min]).
2. Well-controlled blood glucose (glycated hemoglobin <8% on two consecutive occasions) while taking metformin alone or glibenclamide alone.
3. No clinical evidence of acute diabetic complications or major medical illness (e.g., myocardial infarction, heart failure, infection, recent intensive care admission, or injury).

Patients taking antihypertensive or lipid-lowering medications were maintained on stable doses of these medications during the study. All subjects provided informed consent before participation. Patients were divided into two groups according to the antihyperglycemic agents used, either metformin alone or glibenclamide alone. CRP was measured on two separate occasions 4 wk apart and the mean was calculated. Quantitative determination of CRP was done by means of particle enhanced immunoephelometry. The following data were collected from the study groups: age; sex; BMI (calculated by weight in kilograms divided by the height in square meters); duration of diabetes; smoking history; presence of hypertension, hyperlipidemia, and obesity according to the WHO criteria mentioned before; duration of metformin and glibenclamide use; and mean CRP level. The two groups were compared regarding age, sex, BMI, hypertension, hyperlipidemia, and mean CRP level.

Statistical Analyses

Statistical analysis was done using SPSS 9.1. χ^2 was used to analyze group difference for categorical variables. For continuous variable, student's *t*-test was used when comparing two groups. Spearman correlation analysis was performed for comparison of values for CRP, age, and BMI. $p < 0.05$ was considered significant.

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References

1. Kannel, W. B., D'Agostino, R. B., Wilson, P. W., Belanger, A. J., and Gagnon, D. R. (1990). *Am. Heart J.* **120,** 672–676.
2. Usitupa, M. I., Niskanen, L. K., Siitonen, O., Voutilainen, E., and Pyorala, K. (1990). *Circulation* **82,** 27–36.
3. Pyorala, M., Miettinen, H., Halnen, P., Laasko, M., and Pyorala, K. (2000). *Arterioscl. Thromb. Vasc. Biol.* **20,** 538–550.
4. Reaven, G. M. (1988). *Diabetes* **37,** 1595–1607.
5. Haffner, S. M., Valdez, R. A., Hazuda, H. P., Mitchell, B. D., Morales, P. A., and Stern, M. P. (1992). *Diabetes* **41,** 715–722.
6. Haffner, S. M., D'Agostino, R., Mykkanen, L., et al. (1999). *Diabetes Care* **22,** 562–568.
7. Reaven, G. M., Chen, D. I., Jeppersen, J., Maheux, P., and Krauss, R. M. (1993). *J. Clin. Invest.* **92,** 141–146.
8. Jokl, R., Laimins, M., Klein, R., Lyons, T., Lopes-Virella, M., and Colwell, J. (1994). *Diabetes Care* **17,** 818–823.
9. Imperatore, G., Riccardi, G., Lovine, C., Rivellse, A., and Vaccaro, O. (1998). *Diabetes Care* **21,** 649–654.
10. Hak, A. E., Stehouwer, C. D., Bots, M. L., et al. (1999). *Arterioscl. Thromb. Vasc. Biol.* **19,** 1986–1999.
11. Despres, J. P. and Marette, A. (1994). *Curr. Opin. Lipidol.* **5,** 274–289.
12. Despres, J. P., Lamarche, B., Mauriege, P., et al. (1996). *N. Engl. J. Med.* **334,** 952–957.
13. U.K. Prospective Diabetes Study. (1998). *Lancet* **352,** 837–852.
14. Abraira, C., Colwell, J., Nuttall, F., et al. (1997). *Arch. Intern. Med.* **157,** 181–188.
15. Chu, N. V., Caufield, M., Kong, A. P., et al. (2002). *Diabetes Care* **25,** 542–549.
16. Fonseca, V. A., Reynolds, T., Hemphill, D., et al. (1998). *Diabetes Complications* **12,** 181–186.
17. Tack, C. J., Smits, P., Demacker, P. N., and Stalenhoef, A. F. (1998). *Diabetes Care* **21,** 796–799.
18. Minamikawa, J., Tanaka, S., Yamauchi, M., Inoue, D., and Koshiyama, H. (1998). *J. Clin. Endocrinol. Metab.* **83,** 1818–1820.
19. Yudkin, J. S., Panahloo, A., Stehouwer, C., et al. (2000). *Diabetologia* **43(9),** 1099–1106.
20. Baily, C. J. (1992). *Diabetes Care* **15,** 755–772.
21. Groop, L. (1992). *Diabetes Care* **15,** 737–754.
22. Pepys, M. B. (1996). In: *Oxford textbook of medicine*. Warrell, D. A. (ed.). Oxford University Press: New York.
23. McMillan, D. E. (1989). *Metabolism* **38,** 1042–1046.
24. Pickup, J. C., Mattock, M. B., Chusney, G. D., and Burt, D. (1997). *Diabetologia* **40,** 1286–1292.
25. DeFronzo, R. A. and Ferrannini, E. (1991). *Diabetes Care* **14,** 173–194.
26. Kaplan, N. M. (1989). *Arch. Intern. Med.* **149,** 1514–1520.
27. Alberti, K. G. M. M. and Zimmet, P. Z. (1998). *Diabetes Med.* **15,** 539–553.
28. Isomaa, B. O., Lahti, K., Almgren, P., et al. (2001). *Diabetes Care* **24,** 683–689.

29. Tracy, R. P., Psaty, B. M., Macy, E., et al. (1997). *Arterioscl. Thromb. Vasc. Biol.* **17,** 2167–2176.
30. Haverkate, F., Thompson, S. G., Pyke, S. D. M., Gallimore, J. R., and Pepys, M. B. (1997). *Lancet* **349,** 462–466.
31. Koenig, W., Frohlich, M., Sund, M., et al. (1999). *Circulation* **99,** 237–242.
32. Frohlich, M., Boeing, H., Imhof, A., et al. (2000). *Diabetes Care* **12,** 1835–1839.
33. Danesh, J., Muir, J., Wong, Y.-K., Ward, M., Gallimore, J. R., and Pepys, M. B. (1999). *Eur. Heart J.* **20,** 954–959.
34. Kuller, L. H., Tracy, R. P., Shaten, J., Meilah, E. N. (1996). *Am. Epidemiol.* **144,** 537–547.
35. Tracy, R. P., Lemaitre, R. N., Psaty, B. M., et al. (1997). *Arterioscl. Thromb. Vasc. Biol.* **17,** 1121–1127.
36. Lagrand, W. K., Visser, C. A., Hermens, W. T., et al. (1999). *Circulation* **100,** 96–102.
37. Cermak, J., Key, N. S., Bach, R. R., Jacob, H. S., and Vercellotti, G. M. (1993). *Blood* **82,** 513–520.
38. Pepys, M. B., Rowe, I. F., and Baltz, M. L. (1985). *Int. Rev. Exp. Pathol.* **27,** 83–111.
39. Mehta, R. H., Ruane, T. J., McCargar, P. A., Eagle, K. A., and Stalhandsket, E. J. (2000). *Arch. Intern. Med.* **8,** 1301–1306.
40. Ceniceros, I., Gastaldo, R., Cabades, A., and Cebrian, J. (1997). *Med. Clin. (Barc.)* **5,** 171–174.
41. Osztay, K. R. and Korhaza, B. (1999). *Orv. Hetil.* **13,** 1357–1360.
42. Abbud, Z. A., Shindler, D. M., Wilson, A. C., and Kostis, J. B. (1995). *Am. Heart J.* **1,** 51–58.
43. Demirovic, J., Blackburn, H., McGoveern, P. G., Luepker, R., Sprafka, J. M., and Gilbertson, D. (1995). *Am. J. Cardiol.* **16,** 1096–1101.
44. Mendall, M. A., Strachan, D. P., Butland, B. K., et al. (2000). *Eur. Heart J.* **19,** 1584–1590.
45. Eschwege, E., Richard, J. L., and Thibult, N. (1985). *Horm. Metab. Res.* **15,** 41–46.
46. Hayden, C. T. and Reavn, P. D. (2000). *Curr. Opin. Lipidol.* **2,** 519–528.
47. Haffner, S. M., Mykkanen, L., Stern, M. P., Valdez, R. A., Heisserman, J. A., and Bowsher, R. R. (1993). *Diabetes* **42,** 1297–1302.
48. U.K. Prospective Diabetes Study (UKPDS) Group. (1998). *Lancet* **352,** 854–865.