Effects of Gliclazide Versus Metformin on the Clinical Profile and Lipid Peroxidation Markers in Type 2 Diabetes

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The sulfonylurea gliclazide and the biguanide metformin have different mechanisms to reduce glycemia. We performed a randomized study to compare these two agents with respect to glycemic control and effects on lipid peroxidation markers in 36 adult patients with type 2 diabetes. Both agents significantly decreased glycosylated hemoglobin ([HbA_{1c}] $P < .05$), fructosamine ($P < .05$), and the glucose-excursion curve during the oral glucose tolerance test ([OGTT] $P < .01$). With regard to the insulin curve during this test, no significant change was observed with metformin and a significant increase was measured with gliclazide ($P < .05$). Considering the small number of events, no significant difference was detected in the number of hypoglycemic episodes between the two agents. More upper-gastrointestinal (GI) symptoms were observed with metformin compared with gliclazide ($P < .05$). Even with no change in the standard lipid profile, both agents increased serum vitamin E ($P < .01$ for gliclazide and $P < .05$ for metformin) and decreased the level of lipid peroxidation markers in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles ($P < .05$). Despite different mechanisms of action, gliclazide and metformin demonstrated comparable levels of efficacy and complementary effects on lipid peroxidation markers.

TWO CURRENT MEDICATIONS widely used for the treatment of type 2 diabetes mellitus are gliclazide and metformin. Their mechanisms of action to reduce glycemia are different. Gliclazide is a hypoglycemic medication with a primary action to increase insulin secretion from the pancreas[1] by decreasing hepatic glucose production[2] and possibly by increasing glucose transport at the muscle level.[3] Metformin has an antihyperglycemic effect, primarily by reducing hepatic glucose production[4,5] and, to some extent, by increasing glucose transport at the muscle level.[6,7]

Type 2 diabetes has been associated with excessive oxidative stress.[8-10] Gliclazide and metformin have been shown to reduce the damage caused by free radical (FR)-induced activity, including lipid peroxidation. In vitro studies showed that gliclazide scavenges FRs such as superoxide anion (O_2^-), hydroxyl radical ($OH^\cdot$), and nitric oxide ($NO^\cdot$) in a dose-dependent manner,[11] and increases the resistance of low-density lipoprotein (LDL) particles to oxidation[12] as efficiently as ascorbic acid.[13] Interestingly, these studies have also suggested that the capacity of gliclazide to neutralize FRs was independent of the glucose level and seemed specific to this molecule, since glyburide had no measurable effect on FR activity.[11,12] In a clinical study of type 2 diabetic subjects, Periello et al[5] observed that metformin diminishes lipid peroxidation as estimated by indirect calorimetry.

Two clinical studies have made comparisons between gliclazide and metformin.[14,15] The results of both studies demonstrated a similar level of efficacy, with greater insulin secretion with gliclazide, larger weight loss with metformin, and either weight stabilization or gain with gliclazide. However, no specific attention was focused on the side effects profile and the particular effects of these two agents on lipid peroxidation markers. In a similar comparative study, DeFronzo and Goodman[16] showed that glyburide was associated with a higher incidence of hypoglycemic events compared with metformin. Since gliclazide has a lower incidence of hypoglycemic events versus glyburide,[17,18] it is possible that a comparative study between metformin and gliclazide could show different outcomes.

Consequently, the goal of this study is to compare gliclazide and metformin in patients with type 2 diabetes mellitus with regard to the efficacy, side effects profile, and lipid peroxidation markers.

SUBJECTS AND METHODS

Subjects

The study protocol was approved by the Ethics Committee of the Centre de recherche clinique, Centre Universitaire de Santé de l'Estrie (Sherbrooke, Quebec, Canada). Candidates for this study were required to be ambulatory outpatients with no acute cardiovascular or neurologic events in the prior 6 months and no history of neoplastic disease. Patients treated with thiazide, β-blockers, steroids, or insulin or those exposed previously to either gliclazide or metformin were excluded. Oral hypoglycemic medication was withdrawn at least 30 days before randomization. All subjects provided written informed consent before participating in the study.

Experimental Design

Each subject met with a dietitian for dietary assessment 28 days and 14 days before the baseline visit. After baseline assessment, each subject underwent a 3-hour oral glucose tolerance test (OGTT) with 75 g glucose. Each subject was then randomized in an open-label fashion to either gliclazide (Servier Canada, Montreal, Quebec, Canada) or metformin (Hoechst-Marion-Roussel, Montreal, Quebec, Canada). The dose of medication was gradually titrated (increased) to achieve acceptable glycemic control. The desired level of glycemia according to self-monitoring was less than 8.0 mmol/L fasting in the morning and less than 10 mmol/L after meals. Once each subject was maintained on a stable dose of medication, a follow-up visit was then registered at weeks 6, 12, and 18 and the last visit at week 24. The glycosylated hemoglobin (HbA_{1c}) level was measured at baseline, week 12, and week 24. Fructosamine was measured at baseline and weeks 6, 12, 18, and 24.

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Vitamin E and lipid peroxidation parameters were measured at baseline and week 24. The OGTT was repeated at the end of the study (week 24).

OGTT

All subjects consumed a diet containing at least 200 g carbohydrate daily for 3 days preceding each test. Studies were started at 8:30 AM after a 12-hour overnight fast at the Centre de recherche clinique, Centre Universitaire de Santé de l'Estrie. A dose of 75 g glucose was used (Glucodex; Rougier, Quebec, Canada). Blood specimens were drawn at baseline and 30, 60, 90, 120, 150, and 180 minutes for measurement of glucose and insulin levels after oral ingestion of glucose.

Laboratory Parameters

The glucose level was measured by a glucose oxidase colorimetric method (Vitros; Johnson & Johnson Clinical Diagnostics, Rochester, NY), insulin by a radioimmunoassay procedure (Coat-A-Count; Diagnostic Products, Los Angeles, CA), HbA_{1c} (A_{1c}-labile fraction removed) by fast protein liquid chromatography (Pharmacia, Uppsala, Sweden), fructosamine by a colorimetric method (Vitros; Johnson & Johnson Clinical Diagnostics), and lipids by an enzymatic and colorimetric method (Roche Diagnostic Systems, Mississauga, Ontario, Canada). The LDL level was calculated using the Friedewald equation.

Lipoprotein Isolation, Biochemical Markers of Lipid Peroxidation, and Vitamin E Analysis

Acetic acid, sulfuric acid, *n*-butanol, sodium phosphate, thiobarbituric acid, methanol, and hexane were purchased from Fisher (Montreal, Quebec, Canada), and 1,1,3,3-tetraheptoxypropane, D-α-tocopherol, and DL-α-tocopherol were obtained from Sigma (St Louis, MO). Dialysis bags were purchased from Spectrum Medical Industries (Houston, TX). LDL ($1.019 < d < 1.063$) and high-density lipoprotein ([HDL] $1.063 < d < 1.019$) were isolated simultaneously from plasma collected in EDTA (0.4 g/L) according to the method described by Sattler et al.[19] LDL and HDL were dialyzed overnight at 4°C with 10^{-2} mol/L sodium phosphate buffer (pH 7). Concentrations of LDL and HDL solutions were expressed in terms of the total protein concentration (500 μg/mL). Proteins were measured by a commercial assay (Pierce, Rockford, IL). The vitamin E content, thiobarbituric acid–reactive substances (TBARS), and conjugated dienes were analyzed at the same time for each subject 1 day after blood sample collection. To monitor the formation of conjugated dienes, absorbance spectra were recorded between 200 and 700 nm using the phosphate buffer as a reference, with a 1-mm optical pathway. The absorbance level at 234 nm was used to detect the content of conjugated dienes as previously described.[20] TBARS formation in plasma, LDL, and HDL was assayed as described by Yagi,[21] but without precipitation with phosphotungstic acid. TBARS concentrations were calculated as malondialdehyde (MDA) equivalents using the MDA standard curve. MDA was generated by the hydrolysis of 1,1,3,3-tetraethoxypropane. Endogenous vitamin E in plasma, LDL, and HDL was assayed as α-tocopherol by reverse-phase high-performance liquid chromatography, with spectrophotometric detection at 292 nm[22] associated with electrochemical detection as already described.[23]

Clinical Follow-up Study

All patients were encouraged to perform home glucose monitoring during the study. The gliclazide dosage was increased in the following manner: 80, 160, 240, and 320 mg/d divided into two doses with breakfast and supper. The metformin dosage was 750, 1,500, and 2,250 mg/d divided into three doses (one dose with each meal). Once they were on a stable dose of medication, patients were evaluated every 6 weeks for the remainder of the study, and pills were counted at each visit to assess medication compliance.

On each follow-up visit, patients were asked about side effects experienced since the previous visit, with particular attention to gastrointestinal (GI) and hypoglycemic symptoms. A hypoglycemic reaction was diagnosed when the patient developed acute adrenergic and/or neuroglycopenic symptoms that were relieved within 30 minutes by ingestion of food with a carbohydrate content. Patients were asked to measure their blood glucose level during a suspected hypoglycemic event if possible. GI side effects were classified as either upper-GI (ie, dyspepsia, nausea, epigastric discomfort, pyrosis, or loss of appetite) or lower-GI (ie, diarrhea, abdominal bloating, or flatulence). On each follow-up visit, complaints were collected separately for upper-GI and lower-GI symptoms. At the end of the study, the number of complaints was compiled in each category and comparisons were made between the medications. All side effects were reported on a standard written form and subsequently rated by an external rater (P.M.) who was blind to the medication taken by each subject.

Data Analysis

Given the size of our sample, nonparametric procedures were used. For between-group comparisons, continuous variables were analyzed using the Mann-Whitney test for independent samples. Fisher's exact test was used to compare the groups on categorical variables (gender and number of side effects). The Wilcoxon signed-rank test was used for within-group comparisons. When a parameter was measured more than twice during the study, the Friedman test was performed first to assess the time effect. When the result was statistically significant, pairwise comparisons were performed. The total area under the curve (AUC) for glucose and insulin during the OGTT was calculated according to the trapezoidal rule. All data are presented as the mean ± SD. All *P* values are two-tailed tests and *P* less than .05 was considered significant.

RESULTS

Thirty-nine subjects were recruited from a list of patients who previously attended the Diabetes Day Care Center. Groups were comparable at baseline for age, duration of diabetes, female to male ratio (Fisher exact test, $P = .146$), body mass index, and creatinine (Table 1). Three patients were lost to follow-up study after randomization, one in the gliclazide group and two in the metformin group. One patient in the metformin group and the patient in the gliclazide group withdrew from the study because of GI side effects related to the study medication; the other patient in the gliclazide group withdrew for reasons unrelated to the medication. Medication compliance as measured by a pill count was greater than 90% in each subject. At week 24, the mean daily dose for patients on gliclazide was 207 ± 101 mg/d, and for patients on metformin, it was 1,431 ± 611 mg/d. Total daily caloric intake was estimated at baseline using 24-hour recall for food intake; no statistically significant difference was observed between patients in the gliclazide group (1,824 ± 649 kcal/d) compared with the metformin group (1,837 ± 571 kcal/d, $P = .95$).

A small difference was observed at baseline for fasting

Table 1. Subject Characteristics (mean ± SD)

Characteristic	Gliclazide	Metformin
No. of subjects	18	18
Age (yr)	59.3 ± 7.3	59.1 ± 7.1
Diabetes duration (yr)	4.7 ± 6.1	5.4 ± 6.5
Sex ratio (female/male)	8/10	3/15
Body mass index (kg/m²)	28.6 ± 4.0	29.3 ± 3.0
Creatinine (μmol/L)	83 ± 19	83 ± 15

glycemia between groups, with a lower value for the metformin group ($P = .02$; Table 2). However, during the study, both groups experienced a similar reduction of fasting glycemia ($P < .01$) and the AUC for glucose during the OGTT ($P < .01$). No significant change was observed with either of the treatments for fasting insulinemia. At baseline, a trend was noted in the metformin group for a larger AUC for insulinemia during the OGTT ($P = .052$). Gliclazide significantly increased the AUC for insulinemia during the OGTT ($P < .01$). This increase in the AUC for insulinemia during the OGTT was not observed with metformin ($P = .02$ between groups for change from baseline to week 24).

HbA_{1c} and fructosamine levels were comparable between groups at baseline (Table 3 and Fig 1). A significant time effect was observed for HbA_{1c} and fructosamine with both medications according to the Friedman test ($P < .02$). The greater portion of this effect was observed between baseline and week 12 for HbA_{1c} ($P < .01$ for gliclazide and $P < .05$ for metformin) and between baseline and week 6 for fructosamine ($P < .01$). Significant weight loss was observed from baseline to the end of the study with both agents according to the Friedman test ($P < .05$ with gliclazide and $P < .01$ with metformin), but in the gliclazide group, this effect is mainly due to the weight change between baseline and week 12. In this last group, the effect is not maintained at week 24.

During the trial, no significant change was observed in the standard lipid profile including total cholesterol, LDL, HDL, triglycerides, and the LDL/HDL ratio (Table 4). Antioxidant (vitamin E) levels and lipid oxidation markers (conjugated dienes and TBARS) are summarized in Table 5. Serum vitamin E levels significantly increased during the study with both agents ($P < .01$ for gliclazide and $P < .05$ for metformin). For parameters reflecting lipid oxidation, gliclazide significantly decreased the measurable level of conjugated dienes in LDL and HDL ($P < .05$). Metformin decreased the level of conjugated dienes in HDL ($P < .05$) and the TBARS level in serum and LDL ($P < .05$).

The number of hypoglycemic events was not statistically different between groups: eight events were reported in the gliclazide group and three events in the metformin group ($P = .07$; Table 6). For the cumulative number of GI complaints reported during this study per patient, a comparatively lower number was recorded in the gliclazide group for upper-GI complaints ($P = .03$). No difference between the medications was observed for lower-GI symptoms.

Table 2. OGTT Parameters (mean ± SD)

Parameter	Gliclazide	Metformin
Fasting glycemia (mmol/L)		
Baseline	11.3 ± 3.1	9.1 ± 3.5*
Week 24	8.0 ± 3.1†	6.4 ± 1.1†
Fasting insulinemia (pmol/L)		
Baseline	115 ± 72	116 ± 59
Week 24	98 ± 38	99 ± 53
AUC for glucose		
Baseline	18.5 ± 4.3	16.1 ± 4.4
Week 24	14.5 ± 4.0†	12.9 ± 2.3†
AUC for insulin		
Baseline	256 ± 180	383 ± 230
Week 24	361 ± 279†	365 ± 184‡

*$P < .05$ between groups.
†$P < .01$ v baseline in the same group.
‡$P < .05$ between groups for change from baseline.

Table 3. Parameters Related to Metabolic Control (mean ± SD)

Parameters	Gliclazide	Metformin
Fructosamine (μmol/g protein)		
Baseline	4.7 ± 1.3	4.1 ± 0.8
Week 6	4.2 ± 0.9*	3.5 ± 0.6*
Week 12	4.1 ± 0.9*	3.7 ± 0.5*
Week 18	4.0 ± 0.8*	3.7 ± 0.4*
Week 24	4.2 ± 1.0*	3.6 ± 0.4*
HbA_{1c} (%)		
Baseline	7.8 ± 1.8	7.1 ± 1.7
Week 12	6.8 ± 1.5*	6.3 ± 1.1*
Week 24	6.8 ± 1.6*	6.1 ± 0.7*
Weight (kg)		
Baseline	81.9 ± 16.3	84.9 ± 11.1
Week 12	80.9 ± 17.1	83.0 ± 11.2
Week 24	81.5 ± 17.2†	82.3 ± 11.6‡

*$P < .05$ v baseline in the same group.
†$P < .05$, ‡$P < .01$: time effect within group (Friedman test).

DISCUSSION

Treatment of type 2 diabetes is targeted at the basic mechanisms responsible for hyperglycemia, which are a relative deficit in insulin secretion, resistance to its action, and increased hepatic production of glucose.[24] The most important pharmacological effect common to all sulfonylureas is to increase the sensitivity of β cells in the pancreas for insulin secretion following a glycemic stimulus.[25] Differences in the pharmacokinetics between medications in this class have been observed and are related to their mode of excretion and relative half-life.[26] Metformin is a member of the biguanide family. This agent is not effective in the absence of insulin[27] and decreases the glucose excursion during an OGTT with minimal change in the insulin curve.[27,28]

A number of clinical studies have compared sulfonylureas and metformin for the treatment of type 2 diabetes.[14,15,17,29-32] A comparable degree of glycemic control with glyburide and chlorpropamide compared with metformin in monotherapy has been observed.[17,29,31,32] It was also found that the incidence of hypoglycemic events was higher with sulfonylureas compared with metformin.[16,31] The two studies comparing gliclazide and metformin[14,15] did not report hypoglycemic events. All hypoglycemic events reported in the present study were self-managed, limited in time, and without serious clinical consequences. However, the limited number of hypoglycemic events in our relatively small number of patients does not allow us to conclude that the incidence of hypoglycemic events is identical for gliclazide and metformin. According to our observations, one reason for this relatively low incidence of hypoglycemic events with gliclazide may be the absence of an increase in basal insulin as observed by Noury and Nandeuil,[14] which is not the case for another sulfonylurea, chlorpropamide.[33]

Weight stabilization or loss has been observed with metformin treatment.[14-16,29-31] However, in addition to the lack of insulin secretion stimulation by this agent, the variation in body

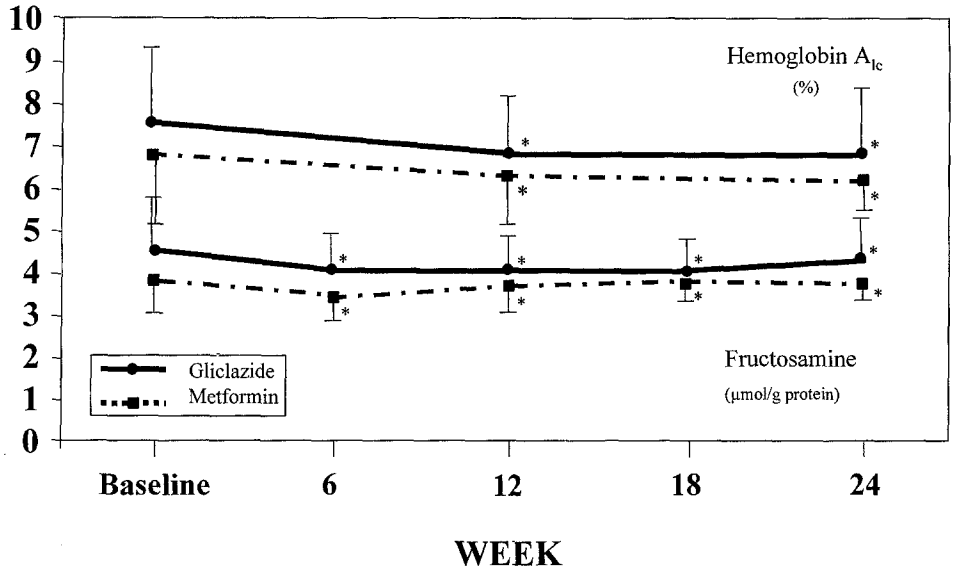

Fig 1. HbA_{1c} and fructosamine levels with gliclazide versus metformin treatment. *$P < .05$ *v* baseline value within group for gliclazide and metformin.

weight is probably dependent on a higher initial weight. We observed a higher incidence of upper-GI complaints in the metformin group, and this may be another factor in the weight loss observed with this agent. The effect of sulfonylureas on weight differs from that of metformin. Campbell et al[30] reported a weight increase with glipizide. McAlpine et al[15] observed a weight increase in patients on gliclazide after exposure to metformin. An absence of significant weight gain with gliclazide has been reported by Noury and Nandeuil[14] and the Diadem Study.[34] Similarly, our study did not observe weight gain in patients treated with gliclazide. In conclusion, even if sulfonylureas have a common pharmacological property in reducing glycemia by stimulating insulin secretion, other mechanisms are probably involved in the modulation of weight.

Improvement in the lipid profile abnormalities associated with type 2 diabetes has been reported with metformin[35-38] and gliclazide.[34,39] This observation is probably dependent on two factors: the degree of glycemic improvement during the treatment phase and the degree of abnormality in the lipid profile pretreatment. Our study failed to show any change in the standard lipid profile with either gliclazide or metformin, despite significant improvement in glycemic levels, and without specific pharmacological intervention to decrease lipids. Our explanation is that the lipid profile was not greatly altered at baseline, and considering our relatively small sample, we did not have the power to detect a significant difference.

Table 4. Serum Lipids (mean ± SD)

Lipid	Gliclazide	Metformin
Total cholesterol (mmol/L)		
Baseline	4.8 ± 0.8	5.4 ± 1.2
Week 24	4.7 ± 0.9	5.3 ± 1.0
LDL cholesterol (mmol/L)		
Baseline	2.8 ± 0.7	3.1 ± 0.9
Week 24	2.7 ± 0.9	3.1 ± 0.8
HDL cholesterol (mmol/L		
Baseline	1.3 ± 0.7	1.0 ± 0.3
Week 24	1.2 ± 0.4	1.1 ± 0.3
Triglycerides (mmol/L)		
Baseline	1.9 ± 0.9	3.7 ± 5.8
Week 24	1.8 ± 0.9	2.3 ± 1.3
LDL/HDL ratio		
Baseline	2.15 ± 1.1	3.1 ± 1.0
Week 24	2.25 ± 1.0	2.8 ± 0.8

Table 5. Lipid Oxidation Parameters (mean ± SD)

Parameter	Gliclazide	Metformin
Vitamin E (μmol/L)		
Serum		
Baseline	23.4 ± 7.4	23.9 ± 8.4
Week 24	30.4 ± 10.2†	27.5 ± 5.7*
LDL		
Baseline	7.9 ± 5.1	7.3 ± 4.4
Week 24	9.3 ± 5.2	8.6 ± 5.4
HDL		
Baseline	2.2 ± 1.3	2.7 ± 3.0
Week 24	2.9 ± 2.2	2.3 ± 1.3
Conjugated dienes (OD at 234 nm)		
Serum		
Baseline	0.26 ± 0.10	0.34 ± 0.16
Week 24	0.25 ± 0.10	0.27 ± 0.16
LDL		
Baseline	0.31 ± 0.16	0.30 ± 0.19
Week 24	0.19 ± 0.13*	0.26 ± 0.16
HDL		
Baseline	0.30 ± 0.51	0.26 ± 0.12
Week 24	0.17 ± 0.20*	0.18 ± 0.13*
TBARS (μmol/L)		
Serum		
Baseline	2.3 ± 3.2	3.5 ± 3.3
Week 24	1.6 ± 1.3	2.2 ± 2.5†
LDL		
Baseline	0.76 ± 0.82	0.73 ± 0.65
Week 24	0.66 ± 0.69	0.65 ± 0.98*
HDL		
Baseline	0.61 ± 0.78	1.6 ± 2.8
Week 24	0.72 ± 1.00	0.7 ± 0.6

*$P < .05$, †$P < .01$: *v* baseline in the same group.

Table 6. Adverse Events

Events	Gliclazide	Metformin
Hypoglycemic events (n)	8	3
Total no. of GI complaints per patient*		
Upper-GI		
No complaint	15	9
1	3	4
2+	0	5†
Lower-GI		
No complaint	14	11
1	3	3
2+	1	4

*From randomization to week 24.

†$P = .03$, with more complaints in the metformin group by Fisher's exact test.

The effect of antidiabetic medication on parameters reflecting the level of antioxidants and lipid peroxidation products is of interest. A body of evidence suggests that hyperglycemia is associated with an oxidative stress at the cellular level and that the intensity of this stress is proportional to the glycemic level.[8-10] Glycation and oxidation of LDL have been proposed to play a significant role in atherosclerosis.[40] The serum level of lipids as measured in a clinical laboratory correlated poorly with markers of lipid peroxidation,[41] in concordance with our results. In vitro studies on oxidative stress showed that gliclazide has multiple effects in its role as a FR scavenger,[11] by diminishing the generation of lipid peroxidation products[12] and by prolonging the time required for oxidation of LDL.[13] Two important points must be emphasized: firstly, these effects are specific to the gliclazide molecule, and secondly, these results are in vitro and thus independent of glycemic fluctuations. To the best of our knowledge, our trial is the first clinical study to support further the evidence that gliclazide is an agent able to reduce oxidative stress in vivo. One probable reason for the observed improvement in the level of lipid peroxidation products with metformin is the improvement in glycemic levels.

Conjugated dienes and TBARS have been proposed in the literature as tools to estimate lipid peroxidation.[42,43] Conjugated dienes are formed early in the oxidation process by removal of a hydrogen atom from a fatty acid chain by a hydroxyl radical ($OH^{\cdot}$). This chain undergoes molecular rearrangement resulting in a conjugated-diene structure.[44] It has been proposed that the measurement of conjugated dienes is a useful index of lipid peroxidation in a pure lipid system[45] as performed with our LDL and HDL preparations. MDA is formed at a later stage during the peroxidation chain reaction. MDA reacts with thiobarbituric acid to form TBARS. The two medications under study had different effects on lipid peroxidation: gliclazide decreased conjugated dienes in LDL and HDL, and metformin decreased conjugated dienes in HDL and TBARS in LDL. This suggests that the two agents probably have different and possibly complementary mechanisms that prevent lipid peroxidation.

Another aspect of LDL oxidation is the protective action of HDL particles. In vitro studies showed that addition of HDL particles inhibited the oxidation of LDL and prevented the sequence of events leading to monocyte adhesion, migration, and differentiation.[46] These effects are not explained by chain-breaking antioxidants present in HDL and are likely to involve primarily two enzymes, paraoxonase and the platelet-activating factor acetylhydrolase.[47,48] Interestingly in our study, a simultaneous reduction of parameters, indicating lipid peroxidation, was observed for LDL and HDL with gliclazide and metformin. In addition to the antioxidant effect observed with the gliclazide molecule in vitro,[11-13] our results are probably also linked to the improvement of diabetic control and the contribution of HDL particles to protect LDL particles against oxidation.

The other aspect of oxidative stress is the reserve available in antioxidants. Type 2 diabetes has been associated with a deficit in vitamin E, known as a chain reaction–breaking antioxidant,[49] and this deficit is further accentuated by hyperglycemia.[50] Vitamin E has also been shown to decrease diacylglycerol levels and to prevent the activation of protein kinase C associated with retinal and renal dysfunction in diabetes.[51] A deficit in vitamin E has been reported as a major determinant of the LDL oxidation lag time,[52] and hyperglycemia has been shown to inhibit the ability of lipids to resist oxidation.[8] In consequence, our hypothesis submits that by decreasing the glycemic level, the level of oxidative stress is diminished and a relative sparing of the antioxidant vitamin E ensues. Vitamin C has also been reported to be lower in patients with type 2 diabetes,[50,53] and we recently observed that this deficit occurs mainly at the cellular level and is accentuated by hyperglycemia.[54] Antioxidants are also interdependent, since vitamin E is regenerated by vitamin C.[55,56] It is also possible that the correction of hyperglycemia has a sparing effect on vitamin C, and this increases the potential to recycle vitamin E.

These observations suggest that type 2 diabetes is characterized by a relative deficit in antioxidants that may result in an acceleration of diabetes-related complications. Our study suggests that improved glycemic control with gliclazide and metformin improves the antioxidant/lipid peroxidation status, and adds further to the argument that improved diabetic control in type 2 diabetes may postpone diabetic complications.

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