Effects of oral antidiabetic drugs over lipid parameters in Turkish type 2 diabetes patients

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Received: 12 November 2008
Accepted: 16 July 2009

Objective. We examined the effects of oral antidiabetics and insulin/insulin analogs over lipid parameters for the first time in Turkish type 2 diabetic (T2DM) patients. **Methods**. A total of 312 T2DM subjects were included within 4 study groups (sulphonylurea, biguanide, insulin/insulin analogs, sulphonylurea+biguanide) in this retrospective study. The demographic, biochemical and clinical data of the patients were evaluated and the study groups were compared for all the variables. The biochemical and lipid parameters were examined in pairs for their correlations for each study group. **Results**. Body mass index (BMI) was found to be lower in the insulin/insulin analogs group in comparison to the biguanide and sulphonylurea+biguanide groups ($p < 0.01$); systolic blood pressure (SBP) was found to be lower in the insulin/insulin analog group in comparison to the sulphonylurea, sulphonylurea+biguanide and biguanide groups ($p < 0.05$); diastolic blood pressure (DBP) was found to be lower in the insulin/insulin analog group in comparison to the biguanide group ($p<0.05$). No difference was found for total-cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol among the study groups ($p>0.05$). Fasting blood glucose and HbA1c levels were found to be lower in the biguanide group when compared to the sulphonylurea and insulin/insulin analogs ($p<0.001$). In all study groups a positive correlation was found between blood glucose and HbA1c levels ($p<0.001$). A weak positive correlation was observed between blood glucose and triglyceride ($p<0.05$) and HbA1c and LDL-cholesterol ($p<0.05$). **Conclusion**. Although no difference persists between the treatment groups for total-cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol, the insulin/insulin analogs seem to lower serum lipids most effectively, which may help prevent coronary events in T2DM patients.

Key Words: Type 2 diabetes, Sulphonylureas, Biguanides, Insulin and analogs, Serum lipids

Introduction

Diabetes is one of the leading causes of morbidity and mortality throughout the world. Approximately 2.2-3% of the world's population suffers from Type 2 diabetes (T2DM) (1). The prevalence of T2DM in Turkish adults was estimated as 2.89 million (11.0%) of the population aged ≥35 years) (2). In T2DM, disturbances of lipid profiles and especially increased susceptibility to lipid peroxidation is observed (3). An increased oxidative stress has been observed in diabetic patients as indicated by high free radical production (4). Although the pathophysiological mechanism of atherosclerosis in diabetic patients has not yet been fully understood, it is thought that hyperlipidemia, increased oxidation of low-density lipoproteins (LDL) and impaired vascular function promote atherogenesis in diabetic patients (5). Glucose deficiency in adipose tissue induces metabolic compensation, leading to the hydrolysis of triglycerides and release of fatty acids, which are oxidized by the liver and transformed to ketonic derivatives (6). In patients with T2DM, besides controlling blood pressure and lipid levels, the major therapeutic goal is to optimize glycaemic control in order to reduce the development and/or severity of long-term diabetic complications (7). Antidiabetic drugs control blood sugar levels in individuals with T2DM (8).

Although oral antidiabetic agents may initially control hyperglycemia, most patients with T2DM will ultimately require insülin therapy, as β-cell function progressively declines (9, 10). Antidiabetic drugs may be subdivided into six groups: sulphonylureas, alpha-glucosidase inhibitors, biguanides, meglitinides, insulin and thiazolidinediones. Sulphonylurea derivatives are class of antidiabetic drugs used in the management of T2DM ("adult-onset"). Biguanides and sulphonylureas are widely used for the treatment of NIDDM and have been used for the prevention of diabetes in non-diabetic patients (11, 12). They act by increasing insulin release from the beta cells in the pancreas. Sulphonylureas [Acetohexamide, Chlorpropamide, Tolbutamide, Tolazamide (tolinase), glipizide (glucotrol), gliclazide, Glibenclamide (glyburide), Gliquidone] act by increasing release from the beta cells. Glimepiride (amaryl) a member of sulphonylurea class, appears to have a useful secondary action in increasing insulin sensitivity in peripheral cells (13). Alpha-glucosidase inhibitors are oral antidiabetic drugs used for T2DM treatment, acting by preventing the digestion of carbohydrates. Alpha-glucosidase inhibitors acarbose (precase), miglitol (glyset), and Voglibase do not enhance insulin secretion but rather inhibit the conversion of disaccharides and complex carbohydrates to glucose. Alpha-glucosidase inhibitor drugs are useful for either monotherapy or in combination therapy with sulphonylureas or other hypoglicemic agents (8, 13). Biguanides form a class of oral hypoglycemic drugs used for diabetes mellitus or prediabetes treatment. Metformin (glucophage, phenformin, buformin) is the only avaliable member of the Biguanide class. Metformin decreases hepatic (liver) glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and use. Metformin may be used as monotherapy (alone) monotherapy, or in combination therapy with a sulphonylurea (8, 13). The meglitinide class of drugs treat T2DM by blocking the potassium channels in beta cells, which closes the ATP-dependent potassium channels and opens the cells calcium channels. The resulting calcium influx causes the cells to secrete insulin. There are two members of the meglitinide class: repaglinide (prandin) and nateglitinide (starlix). The mechanism of the action of the meglitinides is to stimulate insulin production. This activity is both dose dependent and dependent on the presence of low blood

glucose levels. The meglitinides may be used alone or in combination with metformin. The manufacturer warns that nateglinitide should not be used in combination with other drugs that enhance insulin secretion (8, 13). Insulin and insulin analogs (Humulin, Novolin) are responsible for glucose utilization. It is effective in both types of diabetes, since even in insulin resistance, some sensitivity remains and the condition can be treated with larger doses of insulin. Most insulins are now produced by recombinant DNA techniques, and are chemically identical to natural human insulin. Isophane insulin suspension, insulin zinc suspension and other formulations are intended to extend the duration of insulin action and permit glucose control over longer periods of time. An insulin analog is an altered insulin, different from the insulin secreted by the human pancreas, but still avaliable to the human body for performing the same action as human insulin These modifications have been used to create two types of insulin analogs: those that are more readily absorbed from the injection site and therefore act faster than natural insulin, intended to supply the bolus level of insulin needed after a meal: and those that are released slowly over a period of between 8 and 24 hours, intended to supply the basal level of insulin for the day (8, 13). The medication class of thiazolidinedione was introduced in the late 1990s as an adjunctive therapy for T2DM and releated diseases. Rosiglitazone (Avandia) and Pioglitazone (Actos) are members of the thiazolidinediones class. They act by both reducing glucose production in the liver, and increasing insulin dependent glucose uptake in muscle cells.They do not increase insulin production.These drugs may be used in combination with metformin and sulphonylurea.(8, 13).

Material and methods

In this retrospective study the files from between 2003 and 2007 of type 2 diabetic patients were evaluated. An equal number of patients was selected for the study. A total of 2500 files were examined. The metabolic variable levels were recorded from the current treatment, which lasted for at least 6 months. Patients using lipid lowering drugs were excluded from the study. Other blood glucose lowering drugs users (69 patients) such as acarbose, nateglinide or combination uses of these drugs were not included in the study. A total of 312 subjects were included in the study. The 4 study groups were composed of oral antidiabetic sulphonylurea, biguanide users, insulin/insulin analog users and combined oral antidiabetic (sulpho nylurea+biguanide) users. The demographic characteristics (age, gender, height, weight, BMI) were analysed. The biochemical analyses included determination of fasting serum glucose, HbA1c, triglyceride, HDL-cholesterol, LDL-cholesterol, total-cholesterol. The clinical data of the patients, (such as systolic blood pressure, diastolic blood pressure, obesity, hypertension, pulmonary disease, coronary events, family history of diabetes) were also evaluated. All the patients were under hypertensive treatment. The non-hypertensive patients with elevated macroalbuminiria, ACE inhibitors were used to prevent nephropathy.

Statistical analysis

Statistical analyses were conducted using Unistat 5.1 software. All numerical values are reported as means ± SE. A comparison of variables between the four groups was performed using one-way ANOVA. Gender, obesity, hypertension, family history, coronary events and pulmonary disease were estimated by chi-square test. Pearson's correlation coefficient (r) was determined where appropriate. p- values less than 0.05 were considered significant.

Results

The study group comparisons (sulfonlyurea, biguanide, insulin/insulin analogs, sulfonlyurea in combination with biguanide) for each demographic characteristic are shown in Table 1. No significant difference was observed for hypertension, obesity, family history of diabetes, pulmonary disease, and coronary event when the study groups were compared. Body mass index (BMI) was found to be lower in insulin/insulin analogs group in comparison to biguanide and sulphonylurea+biguanide groups ($p < 0.01$); systolic blood pressure (SBP) was found to be lower in insulin/insulin analog group in comparison to sulphonylurea, biguanide and sulphonylurea+biguanide groups ($p < 0.05$); diastolic blood pressure (DBP) was found to be lower in insulin/insulin analog group in comparison to biguanide group ($p < 0.05$) (Table 1). The biochemical characteristics were compared between all the study groups in Table 2. No difference was found for total-cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol among the study groups ($p>0.05$). Fasting blood glucose levels were found to be lower in the biguanide group when compared to sulphonylurea and insulin/insulin analogs ($p < 0.001$). HbA1c levels were found to be lower in the biguanide group when compared to sulphonylurea, sulphonylurea+biguanide and insulin/insulin analogs ($p < 0.001$) (Table 2). Correlations between variable pairs as a function of therapy groups are presented in Table 3. In all study groups a positive correlation was found between fasting blood glucose and HbA1c levels ($p < 0.001$). A weak positive correlation was observed between blood glucose and triglyceride ($p < 0.05$) and HbA1c and LDL-cholesterol ($p < 0.05$) (Table 3).

Table 1 Demographic characteristics comparison of the therapeutic study groups

Demographic characteristics	Sulphonylurea (n)	Biguanide (n)	Insulin and analogs (n)	Sulphonylurea+_ Biguanide (n)	ANOVA p
Age (years)	58.6 ± 1.3 (90)	54.8±1.2 (70)	49.2 ± 1.8^{AD} (70)	57.6±1.1 (77)	< 0.001
Gender (M/F)	39/52	44/27	49/39	34/44	< 0.05
Height (cm)	161.0±1.1 (87)	165.1 ± 1.3^{A} (69)	164.8 ± 1.0 (68)	161.7±1.0 (76)	< 0.05
Weight (kg)	78.0 ±1.7 (87)	86.2±2.1^{ACD} (69)	75.4 ±2.0 (68)	79.2 ±1.5 (76)	< 0.01
BMI (kg/m^2)	30.1 ± 0.6 (87)	31.7 ± 0.7 (69)	27.9 ± 0.7^{BD} (68)	30.3 ±0.5 (76)	< 0.01
Hypertension (No/Yes)	18/35	18/27	10/23	18/34	> 0.05
Obesity (No/Yes)	16/29	12/33	8/22	12/28	> 0.05
Systolic blood pressure (mm Hg)	144.7 ± 3.0 (83)	144.5±2.9 (60)	133.3±2.8^{ABD} (63)	145.2±2.5 (75)	< 0.05
Diastolic blood pressure (mm Hg)	83.6 ± 1.5 (82)	85 ±1.3 (60)	79.1 ±1.4^{B} (63)	83.9 ±1.4 (75)	< 0.05
Family history DM (No/Yes)	13/53	15/42	4/43	8/53	> 0.05
Coronary events (No/Yes)	24/5	29/7	24/2	26/7	> 0.05
Pulmonary Disease (No/Yes)	23/6	30/6	24/1	27/3	> 0.05

$^{A}p < 0.05$ in comparison to sulphonylurea group; $^{B}p < 0.05$ in comparison to biguanide group; $^{C}p<0.05$ in comparison to insulin and analogs group; ^{D} $p<0.05$ in comparison to Sulphonylurea + Biguanide group.

Table 2 Biochemical characteristics comparison of therapeutic study groups

Biochemical characteristics	Sulphonylurea (n)	Biguanide (n)	Insulin and analogs (n)	Sulphonylurea+ Biguanide (n)	ANOVA p
Glucose (mg/dl)	186.2±7.0 (88)	153.45±6.7[AC] (66)	201.87±10.8 (66)	176.21±5.27 (78)	< 0.001
HbA1c %	8.5 ±0.2 (90)	7.01 ±0.2[ACD] (67)	8.60 ±0.3 (68)	8.63 ±0.21 (75)	< 0.001
Total -Cholesterol (mg/dl)	220.1±6.2 (69)	212.1±5.9 (61)	198.2±6.6 (47)	216.48±5.44 (67)	> 0.05
Triglycerides (mg/dl)	206.3±16.7 (67)	195.0±14.4 (60)	152.6±16.0 (44)	179.77±10.23 (64)	> 0.05
HDL-Cholesterol (mg/dl)	48.3 ±1.7 (59)	47.0±1.5 (57)	43.5±1.8 (42)	47.98±1.6 (62)	> 0.05
LDL-Cholesterol (mg/dl)	132.1±5.2 (46)	133.9±6.1 (41)	125.0±6.7 (28)	137.48±5.28 (42)	> 0.05

[A]p < 0.05 in comparison to sulphonylurea group; [B]p < 0.05 in comparison to biguanide group [C]p < 0.05 in comparison to insulin and analogs group [D]p < 0.05 in comparison to sulphonylurea + biguanide group.

Table 3 Pearson's correlation test applied to pairs of variables

Pairs of variables	Sulphonylurea (n)		Biguanide (n)		Insulin and analogs (n)		Sulphonylurea+ Biguanide (n)	
	r	p	r	p	r	p	r	p
Glucose-HbA1c	0.64	< 0.001	0.80	< 0.001	0.56	<0.001	0.52	< 0.001
Glucose- Triglycerides	0.31	< 0.05	-0.04	> 0.05	- 0.14	> 0.05	- 0.12	> 0.05
HbA1c- HDL-Cholesterol	- 0.06	> 0.05	0.26	> 0.05	0.007	> 0.05	- 0.05	> 0.05
HbA1c- LDL-Cholesterol	0.03	> 0.05	0.16	> 0.05	0.47	> 0.05	0.07	> 0.05

Discussion

The purpose of this study was to compare the effects of two oral antidiabetic drug groups, sulphonylureas and biguanides together with insulin and insulin analogs on serum lipid levels in Turkish patients with T2DM. The major therapeutic goal in patients with T2DM is to optimize glycaemic control by controlling blood pressure and lipid levels, in order to reduce the development and/or the severity of long term diabetic complications. The severity of diabetes by the number of oral antidiabetic agents required prior to inclusion and by the large range of HbA1c allowed at inclusion (7). The fasting blood glucose and HbA1c levels of our study groups were above the normal range, demonstrating insufficient glycaemic control (1). The lipid parameters were within the normal range only in the patients using insulin/insulin analogs. In type 2 diabetic groups using oral antidiabetic drugs the lipid levels were higher than normal, which shows that when glycaemic control cannot be reached lipid levels are elevated. Sulphonylureas reduce blood glucose levels by stimulating pancreatic beta cells to secrete insulin, which results in an elevated plasma insulin concentration. A secondary action is the improvement in hepatic and peripheral insulin sensitivity. This effect may be related to hyperglycemia-induced insulin resistance, often referred to as "glucose toxicity," which decreases as the sulphonylureas lower blood glucose levels. Sulphonylureas

alone initially control blood glucose levels in about 50 percent of patients. Sulphonylureas produce a reduction in HbA1c of 1.5 to 2.0 percentage points Their effectiveness declines as the failure of beta cell function progresses, because sulphonylureas are effective only in the presence of a significant residual insulin secretory function. Karlander and collleagues have compared the long-term effect of combined treatment with insulin and glyburide versus insulin alone on serum lipid levels in non-insulin-dependent diabetic (NIDDM) patients with secondary failure to sulphonylurea therapy and found an 11% decrease in HbA1c levels (14). In both groups, there was an increase in high-density lipoprotein cholesterol of approximately 20% lasting throughout the study. There was a decrease in serum cholesterol ($p < 0.05$) and serum triglycerides ($p < 0.05$) in both groups. All changes in lipid variables were comparable in magnitude and duration in both treatments with insulin, and glyburide in NIDDM patients with secondary sulphonylurea failure improves lipid metabolism to a similar degree as insulin therapy alone. In concordance with Karlander et al. (14), the HbA1c levels were not found to differ in the sulphonylurea treated group to that of the other groups in our study. Whereas, although not statistically significant, total-cholesterol, triglyceride, HDL-cholesterol and LDL cholesterol levels were found to be lower in the insulin treated group in comparison to other treatment groups. Decreased levels of plasma glucose due to successful sulphonylurea treatment improve fasting and postprandial hypertriglyceridemia, reduce the number of abnormally small low-density lipoprotein (LDL) particles, and tend to return decreased high-density lipoprotein (HDL) levels to normal (15). This effect of sulphonylureas appears to be secondary to the glucose-lowering effect. Failure to reach target lipid levels would indicate a need for specific pharmacotherapy.

By lowering the daily insulin dose, sulphonylurea drugs appear to improve the sensitivity of exogenous insulin in subjects with type 2 diabetes mellitus manifesting a lapse of glycemic control. Moreover, glimepiride appears to possess a greater insulin-sparing property than other sulphonylureas (16). Drzewoski et al reported a positive correlation between fasting blood glucose and HbA1c (17). Similar to the results of Drzewoski et al, we also demonstrated positive associations between fasting blood glucose and HbA1c in all of the treatment groups analyzed.

In the present study, we observed a weak positive association between fasting blood glucose and triglyceride in the sulphonylurea group, but a weak negative association between fasting blood glucose and HDL-cholesterol. In the insulin/insulin analog treated group a weak positive association between HbA1c and LDL-cholesterol was found. Pasquali et al have shown that metformin can lead to waist circumference reduction (18). The improvement of HbA1c levels in the sample was independent of waist circumference reduction, indicating that metformin improves sensitivity to the action of insulin by mechanisms already described, such as inhibition of hepatic gluconeogenesis (19). Although over half the patients reached HbA1c levels below 8%, only 14% reached ideal metabolic control (HbA1c up to 7%), and 47% kept their HbA1c above 8%. DeWitt et al. have hypothesised that more intensive insulin therapy with fast-acting insulin and self-monitoring might have led to better results (20). The mean fasting blood glucose and HbA1c values of our patients were similar to those reported in other studies (21, 22).

The literature shows discrepant results about the influence of metformin on lipid profile (23). Some studies, in agreement with ours, reported reduction only in TC levels (24, 25), while others reported reduction of TC and TG with an increase of HDL-C

(26, 27). Still other studies showed no changes in lipid profile (28, 29). Another investigation showed an association of metformin with an improvement in the lipid profile even in non-diabetic patients (30). New studies are needed to clarify this issue, since TG and HDL-C are very important parameters for the evaluation of metabolic syndrome.

Yamanouchi et al. compared the metabolic effects of pioglitazone, metformin, and glimepiride in the treatment of Japanese patients with newly diagnosed Type 2 diabetes (31). They reported that the rate of reduction of HbA1c was fastest in patients receiving glimepiride and slowest in patients receiving pioglitazone. Although there were no significant differences among the three groups in HbA1c levels at the end of the study, patients taking pioglitazone had relatively lower fasting plasma glucose levels than patients taking the other two drugs. Our results are not in agreement to Yamanouchi et al since we found the lowest rate of HbA1c in the biguanide treated type 2 diabetic patients .

Long term prospective and randomised studies of the cardiovascular effects of antidiabetic agents in non-diabetic individuals with insulin resistance are lacking. The effect of metformin on systolic and diastolic blood pressures in non-diabetic patients with systemic hypertension is controversial and the long term effect of metformin or glipizide on blood pressure in non-diabetic patients with normal blood pressure is not well known (32, 33). In the present study, subjects taking antihypertensive medication were excluded before entry into the study, and all subjects had arterial blood pressure over normal limits. The sulphonylurea in combination with the biguanide treatment group had the highest level of systolic blood pressure levels, whereas the diastolic blood pressure was found to be the highest in the biguanide group. The systolic blood pressure levels were found to differ in all groups (sulphonylurea, biguanide, sulphonylurea+biguanide) to that of insulin/insulin analogs which also had the lowest level of SBP. Additionally, the DBP was found to differ significantly in the insulin/insulin analogs treated group to that of the biguanide treated group. Individuals in the metformin group had a mild but significant decrease in systolic and diastolic blood pressure during the follow up period. Subjects in the glipizide group also had a non-significant reduction in blood pressure. It is known that glipizide has no effect on lipid profile, whereas metformin may have a favourable effect on plasma cholesterol concentrations (34, 35, 36, 37).

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