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Effect of Lifestyle Modification and Oral Anti-Diabetic Drugs on Metabolic Parameters in Recently Diagnosed Patients with Uncomplicated Type 2 Diabetes Mellitus in Eastern India

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Abstract

BACKGROUND: Oral anti-diabetic drugs (OADs) are often advised for initial treatment for patients with Type 2 Diabetes Mellitus (T2DM). Their effects on glycemic control, lipid profile, insulin resistance and beta cell function has not been systematically studied in India. The objective of this study was to evaluate the effect of lifestyle modification and OADs on metabolic parameters in recently diagnosed uncomplicated T2DM patients. **MATERIAL METHODS:** A total of consecutive sixty four (64) cases of recently diagnosed uncomplicated T2DM in the age group of 30 - 60 years were studied. They were evaluated for weight, body mass index (BMI), fasting plasma glucose (FPG), 2hr post glucose plasma glucose (2hrPGPG), HbA1c, lipid profile, serum fasting insulin, c-peptide, HOMA-IR and HOMA-β. They were divided into four groups according to increasing order of HbA1c values (6.5% - 6.9%, 7% - 7.5%, 7.6% - 8.5%, 8.6% - 8.9%). These four groups were subjected to lifestyle modification (LSM), monotherapy with metformin (1 g) and LSM, dual drug therapy *i.e.* metformin (1 g), glimepiride (1 mg) and LSM, triple drug therapy *i.e.* metformin (1 g), glimepiride 1 mg, sitagliptin 100 mg) and LSM respectively. These patients were followed up after three months of therapy. They were evaluated for the same metabolic parameters and compared with their baseline value. Fourteen (14) patients were lost to follow up. **RESULTS:** We found 91%, 92.8%, 53.3% and 60% of our patients from above four different groups achieved target glycemic control (HbA1c ≤ 6.5%). In all

the four groups, significant improvement in glycemic status, lipid profile, HOMA-IR and HOMA-β were observed (p value < 0.05). **CONCLUSION:** In our study, early Initiation of LSM along with OADs either as monotherapy or in combination therapy according to HbA1c value showed significant improvement in glycemic control, insulin resistance and beta cell function.

Keywords

Type 2 Diabetes Mellitus, Metformin, Glimepiride, Sitagliptin, HOMA-IR, HOMA-β

1. Introduction

India has the second largest number of adults living with diabetes mellitus (DM) worldwide. It has 72.9 million diabetes population with an adult diabetes prevalence rate of 10.4% [1]. Type 2 diabetes (T2DM) is the most common type of diabetes, accounting for around 90% of all cases of diabetes [1]. In T2DM, insulin resistance and relative insulin deficiency leads to increase lipolysis and free fatty acid formation which undergo gluconeogenesis to increase the hepatic glucose output leading to high plasma glucose [2] [3]. Beta cell dysfunction and insulin resistance have complex interrelation for pathogenesis of T2DM. Beta cells function begins to deteriorate well before the diagnosis of T2DM and continue to decline with duration of DM [3] [4]. The evaluation of insulin resistance and beta cells function are measures to assess the status of T2DM. All the microvascular complications results from chronic hyperglycemia. Therefore optimal glycemic control can reduce the risk of diabetic complications [3]. The current American Diabetic Association guidelines [5] for the treatment of T2DM recommend timely stepwise intensification of therapy by adding one or two drug subsequently. But the challenge here is "clinical inertia" defined as the delayed intensification of treatment [6]. This can be solved by early initiation of combination therapy for intensive glycemic control in newly diagnosed T2DM patients. The current American College of endocrinology (ACE) guidelines suggests initial combination therapy for patients with HbA1c ≥ 7.5% [7]. In the context of developing country like India where the majority of the population belongs to low socio-economic status, life long adherence to the treatment is unlikely [8]. In such situation it is very important to select the oral anti-diabetic drugs which are efficacious as well as cost-effective. In our study we are trying to evaluate the glycemic effectiveness of oral anti-diabetic drugs in a single hospital based study.

2. Aim of the Study

This study was carried out to determine the effect of oral anti-diabetic drugs on plasma glucose, lipid profile, insulin resistance and beta cell function in recently diagnosed T2DM patients without any complications.

3. Material and Methods

This study was carried out between the period of July 2017 to December 2017 and was approved by Institutional Ethical Committee, SCB Medical College, Cuttack, Odisha, India. During the study period, sixty four (64) consecutive patients of age 30 - 60 years attended Medicine OPD and Endocrinology OPD of SCB MCH, Cuttack who were recently diagnosed (newly detected or diagnosed within six months) with uncomplicated T2DM and were enrolled for the study. Exclusion criteria are shown in the Table 1.

Consent regarding the study was obtained from patients or their attendants in regional language. Detailed history regarding patient's bio-data, present illness, past illness, personal history, family history was obtained. General and systemic examination was performed. Height was measured by standard stadiometer and weight by standard weighing machine. T2DM was diagnosed according to ADA criteria. Plasma glucose level estimation was done by glucose oxidase method using a standard kit supplied by Acutex Biochemical Pvt. Ltd. (Mumbai, India). Glycosylated haemoglobin (HbA1C) was measured by ion-exchange chromatography method. Lipid profile was done by auto analyser (TBA 120 FR, TOSHIBA) using specific kits. Urine microalbumin was measured by nephelometry. Serum fasting insulin and c-peptide estimation were done by electrochemiluminescence immunoassay (Abbot2000SR analyser). Homeostasis model assessment for insulin resistance (HOMA-IR) and beta cell function (HOMA β) were calculated. HOMA-IR = {fasting serum insulin (uIU/ml) × fasting plasma glucose (mg/dl)}/405. HOMA-β = 360 × fasting serum insulin (uIU/ml)/fasting plasma glucose (mg/dl)-63. Direct and indirect funduscopy was used to rule out retinopathy. Patients with microalbuminuria were ruled out as nephropathy. Neuropathy was ruled out history of paresthesia, numbness and tingling sensation and nerve conduction studies.

These sixty four (64) patients were divided into four groups according to HbA1c values. Each group received different interventions as described in the Table 2.

Table 1. Exclusion criteria in this study.

1	Type 1 diabetes mellitus
2	Gestational diabetes
3	Type-2 diabetes with microvascular complications and acute complications like coronary artery disease, cerebro-vascular accidents
4	Secondary diabetes
5	Type-2 diabetes who are diagnosed more than six month prior to enrollment
6	Type-2 diabetes whose age < 30 yr & age > 60 yr
7	Type-2 diabetes with HbA1c > 9
8	Haemoglobinopathy

Table 2. Different groups according to HbA1c and interventions given.

	HbA1c	No. of patients enrolled	Interventions	No. Of patients on follow up
Group 1	6.5% - 6.9%	14	Lifestyle modifications (LSM) only	11
Group 2	7% - 7.5%.	17	LSM + metformin (1 g)	14
Group 3	7.6% - 8.5%	21	LSM + metformin 1 g, glimepiride 1 mg)	15
Group 4	8.6% - 8.9%	12	LSM + metformin (1 g), glimepiride (1 mg) sitagliptin (100 mg)	10

Total of 64 recently diagnosed uncomplicated Type 2 DM patients were enrolled and out of them, 50 patients came for follow up.

Group 1 included (fourteen) 14 patients with HbA1c value 6.5% - 6.9%. They were subjected to lifestyle modifications (LSM) only. LSM include counselling regarding T2DM and minimum physical activity goal of 150 minutes/week [5]. Group 2 was made of seventeen (17) patients with HbA1c value 7% - 7.5%. They were treated with LSM + metformin (1 g) monotherapy. Group 3 included twenty one (21) patients with HbA1c 7.6% - 8.5% and were treated with LSM+ double drug therapy *i.e.* metformin (1 g) plus glimepiride (1 mg). Group 4 consisting of twelve (12) patients with HbA1c between 8.6% - 8.9% were subjected to LSM and triple drug therapy *i.e.* metformin (1 g), sulfonylurea (glimepiride 1mg) and DPP-4 inhibitor *i.e.* sitagliptin (100 mg). Enrolled patients were educated to maintain a specific diet plan and lifestyle modification which was constant throughout the study. Diet plan was individualised by a registered dietitian using the Diabetes Plate Method. Out of sixty four patients fifty patients came for follow up after 3 months and evaluated for whether they achieved the target HbA1c ≤ 6.5%. Metabolic parameters were measured at baseline and after 3 month of treatment. Statistical analysis was done using SPSS statistical package version 21.0. Quantitative variables were described as mean +/− standard deviation (SD) unless otherwise indicated. Paired t-test was done between baseline and follow up values. For all statistical tests, p value < 0.05 was considered significant.

4. Results

Eleven (11), fourteen (14), fifteen (15) and ten (10) patients came for follow up in group 1, 2, 3 and 4 respectively. **Table 3** shows demographic characteristics of each group. The mean age in these groups were found to be 41.27 ± 7.721, 44.43 ± 9.565, 42.93 ± 8.261, 51.7 ± 6.7.

In Group 1, 91% patients achieved glycemic control target of HbA1c ≤ 6.5%. As shown in the **Table 4**, significant reduction in weight, BMI, FPG, 2 hrPGPG, HbA1c, total cholesterol (TC), triglyceride (TG), LDL, VLDL with mean difference of 2.6 kg, 0.96 kg/m^2, 20.364 mg/dl, 44.27 mg/dl, 0.44%, 12 mg/dl, 17 mg/dl,

Table 3. Demographic profile of study population.

	Male	Female	Total	Mean Age	Mean Weight	Mean BMI
Group 1	9	2	11	41.27 ± 7.721	66.91 ± 7.956	24.48 ± 2.260
Group 2	8	6	14	44.43 ± 9.565	61.64 ± 7.52	23.56 ± 1.43
Group 3	9	6	15	42.93 ± 8.261	66.13 ± 9.203	25.76 ± 2.488
Group 4	7	3	10	51.7 ± 6.700	64.50 ± 8.475	25.24 ± 2.382

Table 4. Comparison between baseline and follow up for Group 1 (HbA1c 6.5% - 6.9% and therapy= LSM only).

	BASELINE n = 11	FOLLOW UP n = 11	p value
WEIGHT	66.91 ± 7.956	64.3 ± 6.63	0.001
BMI	24.48 ± 2.260	23.5 ± 1.73	0.001
FPG	142.91 ± 11.335	122.55 ± 12.210	<0.001
2 hr PGPG	207.09 ± 30.035	162.82 ± 18.088	<0.001
HbA1c	6.77 ± 0 .119	6.33 ± 0.205	<0.001
TOTAL CHOLESTEROL	190.45 ± 27.627	178.45 ± 21.290	0.010
TRIGLYCERIDE	173.73 ± 69.102	156 ± 53.529	0.009
HDL	39.82 ± 6.113	40.91 ± 4.888	0.307
LDL	115.27 ± 19.658	106 ± 13.624	0.027
VLDL	34.91 ± 13.561	31.55 ± 11.219	0.004
SERUM FASTING INSULIN	9.17 ± 2.021	9.873 ± 2.398	0.282
C-PEPTIDE	2.38 ± 0.370	2.268 ± 0.209	0.123
HOMA-IR	3.25 ± 0.843	2.985 ± 0.804	0.045
HOMA-β	41.86 ± 9.138	61.809 ± 17.307	0.001

This table shows significant improvement in all the parameters except HDL, serum fasting insulin and c-peptide.

9.2 mg/dl and 3.3 mg/dl respectively. Mean HDL was increased but not significant. Though Change in serum fasting insulin and c-peptide value were not significant, reduction in insulin resistance (HOMA-IR) and improvement in beta cell function(HOMA-β) were significant with mean difference of 0.2 (p value = 0.045) and 17 (p value = 0.001) respectively.

In group 2, 92.8% patients achieved the glycemic control target HbA1c ≤ 6.5. Table 5 shows change in weight, BMI, FPG, 2hrPGPG, HbA1c, total cholesterol (TC), triglyceride(TG), LDL and VLDL which were significant with mean reduction of 1.14 kg, 0.41 kg/m^2, 23.5 mg/dl, 46.07 mg/dl, 0.86%, 21.43 mg/dl, 19.36 mg/dl, 19.86 mg/dl and 5 mg/dl respectively. Mean HDL increase was 4.79 mg/dl (p value = 0.007). There is no significant change seen in serum fasting insulin and c-peptide level. But there was decrease in HOMA-IR (p value = 0.005) and increase in HOMA-β (p value = 0.001) respectively.

Table 5. Comparison between baseline and follow up for Group 2 (HbA1c 7% - 7.5% and therapy = LSM + Metformin (1 g).

	BASELINE n = 14	FOLLOW UP n = 14	p value
WEIGHT	61.64 ± 7.52	60.5 ± 6.58	0.023
BMI	23.56 ± 1.43	23.16 ± 1.53	0.028
FPG	143.71 ± 18.751	120.21 ± 9.333	<0.001
2 hr PGPG	229.93 ± 31.139	183.86 ± 20.403	<0.001
HbA1c	7.24 ± 0.122	6.379 ± 0.158	<0.001
TOTAL CHOLESTEROL	206.71 ± 34.693	185.29 ± 24.310	0.004
TRIGLYCERIDE	187.86 ± 43.410	168.5 ± 35.87	0.014
HDL	37.43 ± 6.406	42.21 ± 6.411	0.007
LDL	130.64 ± 29.891	110.79 ± 16.757	0.008
VLDL	38.64 ± 8.205	33.64 ± 7.11	0.002
SERUM FASTING INSULIN	9.91 ± 3.779	9.593 ± 3.001	0.446
C-PEPTIDE	2.26 ± 0.336	2.268 ± 0.396	0.923
HOMA-IR	3.44 ± 1.255	2.832 ± 0.891	0.005
HOMA-β	47.81 ± 22.527	62.125 ± 20.643	0.001

This table shows significant improvement in all the parameters except fasting insulin and c-peptide.

In group 3, 53.33% patient achieved the target glycemic control of HbA1c ≤ 6.5. As shown in the Table 6, there was no statistically significant change in weight (p value = 0.238) and BMI (p value = 0.071). FPG, 2hrPGPG and HbA1c improved significantly with mean reduction of 39 mg/dl, 92.26 mg/dl and 1.41% respectively. Significant Mean reduction of 23.6 mg/dl, 48.47 mg/dl, 16.73mg/dl, 10.13 mg/dl were seen in TC, TG, LDL, VLDL respectively. Mean increase in HDL was 2.6 mg/dl which was not significant. Increase with C-peptide level was significant with mean increase of 0.216 and beta cell function (HOMA-β) was increased by 19.25% (p value = 0.001). Both fasting insulin level was decreased (p value = 0.012) and Insulin resistance (HOMA-IR) was decreased (28.5%, p value = 0.005).

In group 4, 60% patients achieved the target HbA1c ≤ 6.5. Reduction in weight and BMI were not significant. Table 7 shows mean reduction in FPG, 2hrPGPG and HbA1c was 31.7 mg/dl (p value < 0.001), 92.1mg/dl (p value < 0.001) and 2.12% (p value < 0.001) respectively. Significant mean reduction in TC, TG, LDL, VLDL were 26.8 mg/dl, 28.5 mg/dl, 25.8 mg/dl, 8.5 mg/dl respectively. Mean increase in HDL was 8.4 mg/dl. (p value = 0.003). There is non-significant increase in c-peptide level. Decrease in fasting insulin level is significant with mean difference of 1.24 (p value = 0.03). Insulin resistance (HOMA-IR) was found to be decreased (p value < 0.001) and beta cell function (HOMA-β) was improved significantly with mean difference of 9.14 (p value = 0.001) respectively.

Table 6. Comparison between baseline and follow up for Group 3 (HbA1c 7.6% - 8.5% and Therapy = LSM + Metformin (1 g) + Glimepiride (1 mg).

	BASELINE n = 15	FOLLOW UP n = 15	p value
WEIGHT	66.13 ± 9.203	65.3 ± 8.8	0.238
BMI	25.76 ± 2.488	25.4 ± 2.47	0.071
FPG	168.00 ± 43.066	129 ± 11.006	0.001
2 hr PGPG	282.47 ± 47.334	190.2 ± 17.905	<0.001
HbA1c	8.01 ± 0.264	6.6 ± 0.256	<0.001
TOTAL CHOLESTEROL	220.00 ± 55.699	196.4 ± 32.924	0.007
TRIGLYCERIDE	223.53 ± 59.705	175.07 ± 29.429	0.002
HDL	38.00 ± 7.378	40.6 ± 5.422	0.063
LDL	137.40 ± 47.596	120.67 ± 26.478	0.040
VLDL	45.27 ± 11.732	35.13 ± 5.902	0.001
SERUM FASTING INSULIN	10.43 ± 2.962	9.353 ± 2.164	0.012
C-PEPTIDE	1.98 ± 0.445	2.186 ± 0.266	0.018
HOMA-IR	4.14 ± .954	2.954 ± 0.605	<0.001
HOMA-β	44.72 ± 26.105	53.333 ± 18.149	0.017

This table shows significant improvement in all the parameters except weight, BMI and HDL.

Table 7. Comparison between baseline and follow up for Group 4(HbA1c 8.6% - 8.9%, Therapy = LSM + Metformin (1 g) + Glimepiride (1 mg) + Sitagliptin (100 mg).

	BASELINE n = 10	FOLLOW UP n = 10	p value
WEIGHT	64.50 ± 8.475	63 ± 7.7	0.066
BMI	25.24 ± 2.382	25 ± 2.04	0.482
FPG	166.90 ± 18.965	135.2 ± 12.848	<0.001
2 hr PGPG	279.60 ± 47.449	187.5 ± 15.813	<0.001
HbA1c	8.75 ± 0.127	6.63 ± 0.309	<0.001
TOTAL CHOLESTEROL	214.20 ± 34.918	187.4 ± 28.422	0.002
TRIGLYCERIDE	183.10 ± 54.089	154.6 ± 45.693	0.021
HDL	36.20 ± 9.114	44.6 ± 8.085	0.003
LDL	137.70 ± 30.346	111.9 ± 18.741	0.001
VLDL	39.40 ± 12.420	30.9 ± 9.597	0.006
SERUM FASTING INSULIN	10.02 ± 10.02	8.78 ± 1.417	0.030
C-PEPTIDE	2.08 ± 0.392	2.165 ± 0.23	0.423
HOMA-IR	4.02 ± .656	2.914 ± 0.427	<0.001
HOMA-β	36.27 ± 9.941	45.421 ± 12.322	0.010

This table shows significant change in all the parameters except weight, BMI and c-peptide.

5. Discussion

Lifestyle modification improved glycemic status, insulin resistance and beta cell function in group 1 patients. Lipid profile was also improved but increase in HDL was not significant. These findings are corroborative with previous studies in Indian population by Deshmukh *et al.* and Sanghani *et al.* [9] [10]. However it differs from a study on Japanese population by Michishita et al where increase in HDL was significant [11]. This is attributed to normal HDL value of our patients at baseline. Ellsworth *et al.* showed in their study that LSM and dietary modification improve insulin resistance [12]. Ramachandran *et al.* in their study of diabetes prevention programme in India found decreased insulin resistance by lifestyle modification [13].

Patients in the group 2 were observed to have significant improvement in all the parameters. A review on metformin by Goley showed that effect of metformin on body weight in various randomized controlled trials was variable, with about half of studies demonstrating significant reductions in body weight with metformin, relative to baseline or comparator [14]. Our study results were in corroboration with a Diabetes Progression Outcomes Trial by Kahn *et al.*, which suggested significant weight loss in patients uncontrolled by lifestyle intervention when subjected to monotherapy with metformin [15]. A meta-analysis thirty five (35) trials by Hirst *et al.* suggested evidence in support of effectiveness of metformin therapy in lowering of HbA1c when used as monotherapy or in combination [16]. It is worth emphasizing that metformin is effective in Asian Indian patients, in lower doses (250 - 1000 mg/day) than is being used in western countries. This could be due to the lower BMI of Asian Indians and/or due to the better efficacy of the drug in this racial group perhaps related to insulin resistance. Results from the study on diabetes population from Andhra Pradesh by Garimella *et al.* are in agreement with our results regarding metformin on lipid profile [17]. Improvement in beta cell function (HOMA-β) and insulin resistance (HOMA-IR) was significant suggesting the role of metformin as insulin sensitizer.

Group-3 patients received lifestyle modification and dual therapy and showed no statistically significant change in weight (p value = 0.238) and BMI (p value = 0.071). Charpentier *et al.* and Gupta *et al.* showed patients on MF and GP demonstrated no change in body weight and BMI at the end of 12 weeks [18] [19]. Improved glycemic parameters were observed similar to studies by Charpentier *et al.,* Ingle *et al.* [18] [20]. This suggest extrapancreatic effects of glimepiride made its combination with metformin more effective in improving glycemic control by reducing glucose level. We differ from studies of Gupta *et al.*, Ingle et al on Indian population regarding HDL which suggested significant increase in HDL [19] [20]. The difference is due to the baseline value of HDL which was normal in our study population. Increase with C-peptide level was significant with mean increase of 0.216 and beta cell function (HOMA-β) was increased by 19.25% (p value = 0.001). Both fasting insulin level was decreased (p value =

0.012) and Insulin resistance (HOMA-IR) was decreased (28.5%, p value = 0.005).

In group-4 patients, reduction in weight and BMI were not significant. A meta-analysis metformin + SU + DPP4i by Downes *et al.* showed significant lowering of body weight [21]. Our results differ in this regard. This is attributed to the higher baseline weight in this group and higher HbA1c patients enrolled in this group. Glycemic control and improved lipid profile was observed similar to studies of by Hermansen *et al.* [22] and M K Moon *et al.* [23] Insulin resistance (HOMA-IR) was found to be decreased (p value < 0.001) and beta cell function (HOMA-β) was improved significantly with mean difference of 9.14 (p value = 0.001) respectively. Addition of sitagliptin to the combination of glimepiride and metformin provided numerically greater improvement in HbA1c.Both metformin and sitagliptin increased active GLP-1, metformin likely operated through increased GLP-1 release and sitagliptin by inhibiting degradation. Hence the combination provided additive effects on GLP-1. This complementary effect of sitagliptin and metformin on increasing GLP-1 levels could provide a basis for explaining the enhanced efficacy observed.

In all the four groups, improvement in HOMA-IR and HOMA-β were significant (p value < 0.05). Lifestyle modification and OADs, either as monotherapy or in combination acts on various pathophysiological mechanism of T2DM and reduces hyperglycemia. Metformin decreases hepatic glucose production from pancreas and increases glucose uptake by peripheral tissue. Glimepiride enhances insulin secretion. Sitagliptin increases insulin secretion and decreases glucagon secretion. These effects of drugs translate into decreased insulin resistance and increase in beta cell function.

6. Conclusion

Early intensive therapy with oral anti-diabetic drugs either alone or in combination as per HbA1c level results in significant control in glycemic status at three (3) months. It improves beta cell function and insulin resistance. This improvement will contribute to the legacy effect which subsequently decreases the microvascular complications in long run. However the present study has its own limitation being a clinical study and conducted only in the eastern part of India which may not represent whole of India. A multicentric study with large number of patient from different parts of India is required to consolidate our findings.

References

[1] International Diabetes Federation (2017) IDF Diabetes Atlas. 8th Edition, International Diabetes Federation, Brussels, 78.

[2] Gerich, J.E. (2003) Contributions of Insulin-Resistance and Insulin-Secretory Defects to the Pathogenesis of Type 2 Diabetes Mellitus. *Mayo Clinic Proceedings*, **78**, 447-456. https://doi.org/10.4065/78.4.447

[3] UK Prospective Diabetes Study Group (1995) U.K Prospective Study-16. Overview of 6 Years' Therapy of Type-II Diabetes: A Progressive Disease. *Diabetes*, **44**,

1249-1258. https://doi.org/10.2337/diab.44.11.1249

[4] Festa, A., Williams, K., D'Agostino, R., Wagenknecht, L.E. and Haffner, S.M. (2006) The Natural Course of Beta-Cell Function in Nondiabetic and Diabetic Individuals: The Insulin Resistance Atherosclerosis Study. *Diabetes*, **55**, 1114-1120. https://doi.org/10.2337/diabetes.55.04.06.db05-1100

[5] American Diabetes Association (2016) Approaches to Glycemic Treatment. *Diabetes Care*, **39**, S52-S59. https://doi.org/10.2337/dc16-S010

[6] Khunti, K., Wolden, M.L., Thorsted, B.L., Andersen, M. and Davies, M.J. (2013) Clinical Inertia in People with Type 2 Diabetes: A Retrospective Cohort Study of More than 80,000 People. *Diabetes Care*, **36**, 3411-3417. https://doi.org/10.2337/dc13-0331

[7] Garber, A.J., Abrahamson, M.J., Barzilay, J.I., *et al.* (2017) Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm—2017 Executive Summary. *Endocrine Practice*, **23**, 207-238. https://doi.org/10.4158/EP161682.CS

[8] Sharma, T., Kalra, J., Dhasmana, D.C. and Basera, H. (2014) Poor Adherence to Treatment: A Major Challenge in Diabetes. *Journal of Immunology and Clinical Microbiology*, **15**, 26-29.

[9] Deshmukh, S.M., Mani, U.V., Desai, S.A., lyer, U.M., Patel, R.P. and Sen, A.K. (2000) Lifestyle Modifications on Control of Diabetes Mellitus. *International Journal of Diabetes in Developing Countries*, **30**, 89-97.

[10] Sanghani, N.B., Parchwani, D.N., Palandurkar, K.M., Shah, A.M. and Dhanani, J.V. (2013) Impact of Lifestyle Modification on Glycemic Control in Patients with Type 2 Diabetes Mellitus. *Journal of Clinical Endocrinology and Metabolism*, **17**, 1030-1039.

[11] Michishita, R., Tanaka, H., Kumahara, H., Ayabe, M., Tobina, T., Yoshimura, E., Matsuda, T., Higaki, Y. and Kiyonaga, A. (2014) Effects of Lifestyle Modifications on Improvement in the Blood Lipid Profiles in Patients with Dyslipidemia. *Journal of Metabolic Syndrome*, **3**, 150. https://doi.org/10.4172/2167-0943.1000150

[12] Ellsworth, D.L., Costantino, N.S., Blackburn, H.L., Engler, R.J.M., Kashani, M. and Vernalis, M.N. (2016) Lifestyle Modification Interventions Differing in Intensity and Dietary Stringency Improve Insulin Resistance through Changes in Lipoprotein Profiles. *Obesity Science & Practice*, **2**, 282-292. https://doi.org/10.1002/osp4.54

[13] Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A.D. and Vijay, V. (2006) The Indian Diabetes Prevention Programme Shows That Lifestyle Modification and Metformin Prevent Type 2 Diabetes in Asian Indian Subjects with Impaired Glucose Tolerance. *Diabetologia*, **49**, 289-297. https://doi.org/10.1007/s00125-005-0097-z

[14] Golay, A. (2008) Metformin and Body Weight. *International Journal of Obesity*, **32**, 61-72. https://doi.org/10.1038/sj.ijo.0803695

[15] Kahn, S.E., Haffner, S.M., Heise, M.A., Herman, W.H., Holman, R.R., Jones, N.P., *et al.* (2006) Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *The New England Journal of Medicine*, **355**, 2427-2443. https://doi.org/10.1056/NEJMoa066224

[16] Hirst, J.A., Farmer, A.J., Ali, R., Roberts, N.W. and Stevens, R.J. (2012) Quantifying the Effect of Metformin Treatment and Dose on Glycemic Control. *Diabetes Care*, **35**, 446-454. https://doi.org/10.2337/dc11-1465

[17] Garimella, S., Seshayamma, V., Rao, H.J., Kumar, S., Kumar, U. and Saheb, H.S. (2016) Effect of Metformin on Lipid Profile of Type II Diabetes. *International Journal of Integrative Medical Sciences*, **3**, 449-453.

[18] Charpentier, G., Fleury, F., Kabir, M., Vaur, L. and Halimi, S. (2001) Improved Glycaemic Control by Addition of Glimepiride to Metformin Monotherapy in Type 2 Diabetic Patients. *Diabetic Medicine*, **18**, 828-834. https://doi.org/10.1046/j.1464-5491.2001.00582.x

[19] Gupta, S., Khajuria, V., Tandon, V.R., Mahajan, A. and Gillani, Z.H. (2015) Comparative Evaluation of Efficacy and Safety of Combination of Metformin-Vidagliptin versus Metfromin-Glimepiride in Most Frequently Used Doses in Patients of Type 2 Diabetes Mellitus with Inadequately Controlled Metformin Monotherapy—A Randomised Open Label Study. *Perspectives in Clinical Research*, **6**, 163-168. https://doi.org/10.4103/2229-3485.159942

[20] Ingle, P.V. and Talele, G.S. (2011) Comparative Effects of Metformin in Combination with Glimepiride and Glibenclamide on Lipid Profile in Indian Patients with Type 2 Diabetes Mellitus. *International Journal of Pharmaceutical Sciences and Research*, **3**, 472-474.

[21] Downes, M.J., Bettington, E.K., Gunton, J.E. and Turkstra, E. (2015) Triple Therapy in Type 2 Diabetes; A Systematic Review and Network Meta-Analysis. *PeerJ*, **3**, e1461. https://doi.org/10.7717/peerj.1461

[22] Hermansen, K., Kipnes, M., Luo, E., Fanurik, D., Khatami, H. and Stein, P. (2007) Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor, Sitagliptin, in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Glimepiride Alone or on Glimepiride and Metformin. *Diabetes, Obesity and Metabolism*, **9**, 733-745. https://doi.org/10.1111/j.1463-1326.2007.00744.x

[23] Moon, M.K., Hur, K.-Y., Ko, S.-H., *et al.* (2017) Combination Therapy of Oral Hypoglycemic Agents in Patients with Type 2 Diabetes Mellitus. *Diabetes & Metabolism Journal*, **41**, 357-366. https://doi.org/10.4093/dmj.2017.41.5.357