Treatment Using a Combination of Oral Anti-hyperglycemic Agents in Type 2 Diabetes Mellitus

Harsinen Sanusi

ABSTRACT

Up to this moment, there are various oral anti-hyperglycemic (OAH) known, such as the insulin secretagogue group of drugs, which in essence aims to increase insulin secretion by β pancreatic cells, and the group of drugs that increases tissue sensitivity to insulin. Administration of a single drug from one of these two groups will eventually fail to achieve euglycemic control level. Instead, a combination of two kinds of OAH with different mechanism of action has been proven to significantly achieve glycemic control compared to administration of a single agent. In addition to reducing side effects, administration of a combination of two kinds of OAH can also postpone the need for insulin, which is generally disliked by patients. Sulphonilurea and metformin are among the most common drugs to be combined, but other combinations could also produce the same satisfactory effect. Combination of sulphonilurea and troglitazone does not produce expected euglycemic effect, even though it can reduce the HbA1c level.

Administration of 3 types of OAH is not advisable, since generally, a combination of 2 kinds of drugs at maximum dose could no longer achieve glycemic control, even with the addition of another OAH. In addition to more side effects and higher cost, such treatment is not practical, and insulin secretion by beta cells generally can no longer be increased. Patients that fail to demonstrate satisfactory results with a combination of 2 types of OAHs are advised to be treated with moderate-acting insulin at night as an additional treatment, with a dose titered to achieve euglycemic control. Patients receiving single treatment that could not achieve euglycemic control may receive combined treatment before reaching the maximum dose, since at maximum dose, there is generally more side-effects.

Division of Metabolism and Endocrinology, Department of Internal Medicine, Faculty of Medicine of The University of Hasanuddin/Dr. Wahidin Sudirohusodo General Central Hospital, Makassar, South Sulawesi, Indonesia

INTRODUCTION

Up to now, there are various oral-antihyperglycemic drugs for the treatment of diabetes mellitus, aimed at reducing the degree of hyperglycemia. However, the benefits of the administration of a combination of these drugs have rarely been discussed. OAH agents generally function to increase insulin secretion (insulin secretagogue agents) or increase the sensitivity of peripheral tissue towards insulin (non-secretagogue).[1,2,3,4] Considering the difference in the mechanisms of action of these drugs, it makes sense that the administration of a combination of the drugs should be able to produce a greater effect compared to the administration of a single drug.[5] Management of type 2 diabetes mellitus includes dietary regulation, physical exercise, counseling, OAH, and insulin. Research shows that only 10% of patients succeed through dietary regulation, physical training, and counseling, while only 10% require insulin. The remaining 80% require OAH.[5] In general, treatment with OAHs is immediately initiated after the diagnosis of diabetes mellitus is established.[6] The use of sulphonilurea as a single treatment still dominates the management of diabetes mellitus. However, research demonstrates that administration of sulphonilurea produces a primary or secondary failure rate of 5-10% every year. The mean plasma glucose level will return to its initial point after 5 years of treatment, and it is not uncommon for patients who have just been diagnosed with type 2 diabetes mellitus with a fasting plasma glucose level of over 200 mg% to not reach the euglycemic control level with the administration a single agent.[6] Insulin would thus be required to achieve the euglycemic control. Normally, prior to the administration of insulin, treatment with another type of OAH with a different mechanism of action is administered in combination with the initial OAH.[6] Every combination of 2 OAH is expected to achieve a synergistic effect or improvement in reducing plasma glucose, with minimum side effects and a better outcome.[6]

The UK Prospective Diabetes Study (UKPDS) clearly demonstrated the progress of disease in the 4209 study subjects receiving intensive treatment with a single OAH.[6] Administration of a single OAH in an obese patient with type 2 diabetes mellitus usually starts with metformin, while those with normal bodyweights or non-obese patients usually are started on sulphonilurea. Treatment combinations for obese and non-obese type 2 diabetes mellitus are principally the same, as long as the two drugs have a different mechanism of action.

BLOOD GLUCOSE REGULATION AND THE PATHOGENESIS OF TYPE-2 DIABETES

Up to now, the pathogenesis of type 2 diabetes mellitus has not been fully discovered. It is still unclear which step is responsible for the initiation of the whole process. This is in contrary to type 1 diabetes mellitus, which is mostly caused by autoimmune processes, while the remaining few have no clear etiology.[2,3,4] Under normal conditions, the body continues to maintain plasma glucose level within normal limits. Three organs that play the most important role in regulating plasma glucose level: the β cell of the pancreas, which produces insulin to reduce blood glucose; the liver, which increases plasma glucose through glycogenolysis and gluconeogenesis; and muscles, that reduce plasma glucose by increasing glucose uptake.[4,5] During fasting, glucose requirement is fulfilled by the liver, through a process known as the liver glucose production (thus producing endogenous glucose). After meals, blood glucose originates from absorbed foods (exogenous glucose). Following meals, most plasma glucose will enter body tissues such as muscles, liver, fat, while the remaining glucose enters non-insulin-sensitive tissues such as the brain, intestines, and red blood cells.[1,2,3,4] Insulin is the main factor in maintaining blood glucose level at approximately 70-120 mg/dl. Insulin acts to stimulate glucose intake at the peripherals, particularly in the muscle cells. Insulin suppresses the synthesis or release of glucose by the liver. In other words, insulin suppresses gluconeogenesis and glycogenolysis.[4,5,6] In type 2 diabetes mellitus, it is unclear whether the initiating process is disturbed insulin secretion by pancreatic β cells or reduced sensitivity of peripheral tissues (insulin-resistance). However, in type 2 diabetes mellitus with clear clinical findings, the two conditions are found hand in hand.[5,6]

CLASSIFICATION OF OAHs

During the last several years, several new types of OAH have been found, such as acarbose, repaglinide, nateglinide, and thiazolidinedione,[5] thus reducing the domination of sulphonilurea. According to its mechanism of action, OAH can be classified into 4 groups:[5]

1. Drugs that inhibit carbohydrate absorption in the intestines: α-glucosidase inhibitors (acarbose)
2. Drugs that stimulate insulin secretion (insulin secretagogues)
   a. Sulphonilurea (glibenclamide, gluquidone, gliclazide, glipizide, glimepiride)
   b. Non-sulphonilurea (repaglinide, nateglinide, meglitinide)
3. Drugs that inhibit glucose production in the liver (metformin–glucophage, metformin HCl)
4. Drugs that increase glucose uptake in peripheral tissues (thiazolidinedione, metformin, and sulphonilurea)

If we analyze the mechanism of action of each group of drugs, we will find that sulphonilurea particularly acts by increasing insulin secretion on pancreatic β cells by inhibiting and blocking ATP-dependent K channels, thus reducing K efflux, causing potassium retention, and causing depolarization that opens Ca++ channels, causing an increase in Ca++ influx, thus causing exocytosis of insulin granules and increasing insulin secretion. In addition, sulphonilurea may function to inhibit α cells from secreting glucagons, and stimulating δ cells to increase secretion of somatostatin, which is a glucagons inhibitor.[1,2,4,7,8] Glimepiride is a drug from the sulphonilurea group that is known as a third generation sulphonilurea for its advanced ability from its predecessors. In addition to increasing insulin secretion, it is also able to increase glucose uptake in the peripheral tissues by increasing GLUT 4 translocation to facilitate glucose entry to the cell. It also produces minimum hypoglycemic effect and does not cause peripheral vasoconstriction.[9] Drugs from the non-sulphonilurea group, such as repaglinide and nateglinide, have separate receptor sites from sulphonilureas, and do not directly stimulate insulin exocytosis in increasing insulin secretion. This drug is known as "Prandial Glucose Regulators", thus engendering the "one meal" concept, and the "one dose" and "no meal no dose" concepts.[10,11,12] Repaglinide is a novel OAH with a unique molecular structure, mechanism of action, and excretion. Even though it does not belong in the sulphonilurea group, it is classified into the insulin secretagogue group due to its mechanism of action to stimulate insulin secretion from the pancreatic β cell. However, it has a short half-life, and most are not ex-

creted by the kidneys, and is easily absorbed.[13,14,15,16] Unlike sulphonilurea, metformin does not increase insulin secretion at the pancreatic β cells, but instead works particularly by inhibiting glucose production by the liver by suppressing gluconeogenesis and glycogenolysis. In addition, metformin works in peripheral tissues by increasing glucose uptake and inhibiting glucose absorption in the intestines.[13] Alpha-glucosidase inhibitors (acarbose) reduce postprandial plasma glucose level by delaying carbohydrate absorption in the intestines and sparing insulin use.[14] Thiazolidinedione, specifically troglitazone, rosiglitazone, and pyoglitazone, are new drugs introduced as "insulin sensitizers" that increase insulin sensitivity of the liver as well as other organs, and the skeletal muscles.

TREATMENT COMBINATIONS

From the various OAH currently known, it is very rational to combine two types of OAH with different mechanisms of action to produce a better glycemic control effect compared with treatment with a single drug.[5,7] Sulphonilurea has been proven to require a larger dose at use, and it is very possible that at one point the blood glucose level can no longer be controlled at a maximum dose (secondary failure). This is due to the inability of beta cells to further increase insulin secretion. In addition, insulin resistance gradually increases.[13] Initially, OAHs are administered in combination only after a type of OAH has been administered at a maximum dose without being able to control plasma glucose level, thus requiring an additional OAH with a different mechanism of action from the initial OAH. Both sulphonilurea and metformin gradually require increased dosage to achieve euglycemic control level, thus increasing side effects.[13] Like other drugs, OAHs achieve near maximum effect with a dose half the maximum dose. If the drug is administered at maximum dose, it will produce more side-effects. Thus, before reaching maximum dose with a single drug, we could add a second type of OAH to avoid side effects. OAH treatment combination can be administered earlier at a smaller dose based on disturbed insulin secretion and disturbed insulin resistance. A study by the American Diabetes Association (ADA) recommends intensive OAH treatment in type-2 diabetes mellitus patients with an HbAic level of more than 8%, with a glycemic control target of HbA1c < 7%.[16]

Several possible OAH treatment combinations are as follows:[5,17]

1. Sulphonilurea and metformin
2. Sulphonilurea and α-glucosidase inhibitor (acarbose)
3. Sulphonilurea and repaglinide/nateglinide
4. Sulphonilurea and thiazolidinedione
5. Metformin and repaglinide/nateglinide
6. Metformin and acarbose
7. Metformin and thiazolidinedione
8. Nateglinide and thiazolidinedione

1. Sulphonilurea and Metformin

Sulphonilurea and metformin work in synergism. The combination is tolerable, and improves the glycemic control and lipid level in type 2 diabetes mellitus that cannot be controlled through dietary regulation and sulphonilurea.[3,4,6] In the United States, the use of sulphonilurea in type 2 diabetes mellitus is generally the first choice OAH. However, it turned out that sulphonilurea produces an initial failure rate of 30%, while the remaining 70% is successful at the beginning of treatment, but is followed by an annual failure rate of 4-5%. It turned out that combination with metformin can produce glucemic control effect, and is generally safer due to a difference in the mechanism of action. Metformin reduces blood glucose by reducing liver glucose production and increasing glucose uptake in peripheral tissues, while sulphonilurea increases insulin secretion.[3,4,5] Lipid levels drop as when metformin is administered as a single drug.

Likewise, even though there is increased danger of lactic acidosis, the condition is the same as if it was given as a single drug.[6] In a randomized, double-blind, controlled clinical trial on 632 patients with a fasting blood glucose level of over 250 mg%, and a HbAic of 8.8%, administration of glyburide (glibenclamide) and metformin for 6 months produced improved fasting plasma glucose level and HbA1c. However, the difference is more apparent if stated that treatment combination of glyburide and metformin was able to reduce plasma glucose, HbA1c, and plasma lipid level twofolds.[18] Likewise, the UKPDS study on 591 patients with poor control using single treatment demonstrated a reduction in fasting blood glucose of 30%, and 0.5% in HbA1c after the addition of metformin, which is incredibly significant compared to the results from administration of a single agent.[6,13] Combination of sulphonilurea and metformin also demonstrated reduced hypoglycemic symptoms, and did not increase bodyweight compared to the administration of sulphonilurea alone. Combination of sulphonilurea and metformin also reduced the incidence of gastrointestinal symptoms usually common in patients receiving metformin.[6]

2. Sulphonylurea and alpha-glucosidase inhibitor (acarbose)

Administration of acarbose in type-2 diabetes mellitus patients receiving sulphonilurea produces the additional effect in reducing plasma glucose level, particularly postprandial blood glucose, compared to administration of sulphonilurea and metformin in combination.[16,19] Patients with secondary failure are recommended for acarbose type OAH to delay insulin administration. It has been demonstrated that insulin requirement is reduced after administration of acarbose in several patients.[18] Even though acarbose or miglitol is not an "insulin sensitizer", it assists insulin action by directly delaying prandial glucose absorption and reducing the amount of postprandial insulin requirement. Thus, combination of sulphonilurea and acarbose improves fasting and postprandial blood glucose.[16,18] A multi-center, double-blind, cross-over study demonstrated that a combination of sulphonilurea and acarbose is more able to reduce blood glucose and HbA1c compared to sulphonilurea and placebo.[21,22]

3. Sulphonylurea and Repaglinide/Nateglinide

A prospective, multi-center, 1-year, double-blind study demonstrated that repaglinide is just as effective as sulphonilurea in the management of type 2 diabetes mellitus. Even though repaglinide and sulphonilurea has the same mechanism of action as insulin secretagogues, the two drugs may be combined based on the fact that they have separate receptor sites on the pancreatic beta cell, and does not accelerate the cell by means of direct exocytosis of insulin.[7] Thus, theoretically, repaglinide can be combined with sulphonilurea, even though further investigation is required.[7]

4. Sulphonylurea and Thiazolidinedione

Combination of sulphonilurea and thiazolidinedione acts synergistically to reach glycemic control in type 2 diabetes mellitus, and has been proven to be just as effective as combination of sulphonilurea and metformin.[17] In a double-blind clinical trial with placebo control, 552 patients with uncontrolled type-2 diabetes mellitus receiving 12 mg of daily glibenclamide were given an additional 400 mg of troglitazone daily. The study demonstrated a 15% reduction of fasting plasma glucose.[23,24] When compared, combination of sulphonilurea with troglitazone, metformin, or acarbose are all able to produce a significant reduction of HbA1c compared to administration of sulphonilurea alone. However, it has been demonstrated that combination of sulphonilurea and metformin or acarbose produced a reduction of HbA1c to the target of HbA1c 7%. On the other hand, combination of sulphonilurea and troglitazone was not able to produce the expected euglycemic control target.[16]

5. Metformin and Repaglinide/Nateglinide

In a 3 month study, a combination of repaglinide and metformin was able to reduce HbA1c from 8.3% to 6.9% ($p < 0.002$) and fasting blood glucose level from 10.2 to 8.0 mmol/l ($p<0.001$). While if the two drugs were administered separately, they were not able to reduce fasting blood glucose or HbA1c.[16,25] Treatment combination of repaglinide and metformin is three times more effective compared to single therapy, with less or reduced side effects such as gastrointestinal disturbance and hypoglycemia.[25] A study by Horton et al demonstrated that nateglinide is more effective when combined with metformin, and the two complement each other in improving glycemic control in type 2 diabetes. Nateglinide reduces postprandial hyperglycemia. Treatment with nateglinide alone produced a 0.5% reduction of HbA1c. Treatment with metformin alone produced a 0.8% reduction of HbA1c, while combination of nateglinide and metformin produced an HbA1c reduction of 1.4%. Thus, it was demonstrated that a combination of the two drugs were able to produce a significant reduction in HbA1c, as well as increased body weight and minimum episode of hypoglycemia.[11] A study on 467 patients with type 2 diabetes mellitus who did not succeed with daily administration of >1500 mg of metformin, it was demonstrated that the addition of 60-120 mg of nateglinide daily for 24 weeks produced a significant reduction of fasting plasma glucose and HbA1c.[23]

6. Metformin and Acarbose

The addition of acarbose in patients with type 2 diabetes mellitus who did not demonstrate satisfactory results with metformin demonstrated more significant improvement to that in patients receiving sulphonilurea. A 52-week study demonstrated a reduction of HbAic 0.8%.[14,22] Acarbose has a different mechanism of action with other OAHs in reducing plasma glucose.[14] Data from a double-blind one-year study with placebo control demonstrated that a combination of metformin and acarbose produced a significant reduction in postprandial plasma glucose level.[18,19]

7. Metformin and Thiazolidinedione

When metformin and thiazolidinedione are combined, they complement each other, particularly in patients with type 2 diabetes mellitus dominated by insulin resistance. Metformin suppresses glucose production in the liver, and thiazolidinediones, particularly troglitazone, has a

receptor to increase glucose uptake in the muscles.[22] A study demonstrated a significant reduction in fasting plasma glucose level as well as 2 hour postprandial glucose level of 20% and 25% respectively, and an average reduction in HbA1c of 1.2% after six months administration of this combination, compared to when each drug was administered separately.[23] It has also been concluded that a combination of metformin and troglitazone is most recommended for obese type-2 diabetes mellitus patients, since the two drugs reduce the influence of insulin resistance.[24,25]

8. Nateglinide and Thiazolidinedione

A multi-center study on 256 patients with type-2 diabetes mellitus for 33 weeks demonstrated that a combination of repaglinide and troglitazone significantly reduced HbA1c from 8.9 to 7.9% after 14 weeks of treatment. On the other hand, patients receiving troglitazone alone demonstrated an increase from 8.6% to 8.7% instead.[10] Thus, it can be concluded that a combination of repaglinide and troglitazone works in synergy, and is thus more effective than administration of a single agent. No hypoglycemia was found during the course of the study.[10,24] A double-blind randomized study was conducted on 148 patients receiving placebo, 150 patients receiving 120 mg of nateglinide before meals 3 times daily, 151 patients receiving 600 mg of troglitazone, and 150 patients receiving combined treatment of nateglinide and troglitazone. After 16 weeks of treatment, there was a significant reduction in fasting blood glucose and HbA1c in subjects receiving combined treatment compared to those receiving placebo, as well as in the baseline value of those receiving nateglinide or troglitazone. On the other hand, treatment combination of nateglinide and troglitazone significantly reduced fasting blood sugar and HbA1c compared to administration of a single drug ($p<0.001$).[12] Raskin then studied 85 patients receiving troglitazone, 83 patients receiving repaglinide, and 88 patients receiving treatment combination of troglitazone and repaglinide for 22 weeks. The final results demonstrated that the euglycemic control in patients receiving repaglinide was better than those receiving troglitazone alone, and those receiving combined treatment of repaglinide and troglitazone demonstrated even better euglycemic control compared to single administration.[26] A combination of 3 or 4 types of OAHs with different mechanisms of action, such as sulphonilurea, metformin, and alpha glucosidase inhibitor (acarbose), and thiazolidinedione theoretically could be used to avoid the use of insulin in type 2 diabetes mellitus. However, this is yet to be supported by data. In addition, the use of 3 or 4 types of OAH costs, produces more side-effects, and is generally impractical.[21] Furthermore, beta cells would no longer be able to increase insulin secretion.[21]

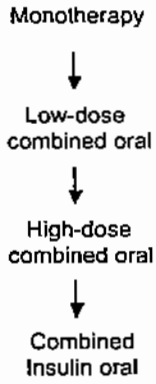

Figure 1. Algorithm of Treatment of Type 2 Diabetes Mellitus

The question is, when can we start administering OAHs in combination? The FDA accepted algorithm of treatment in patients with newly diagnosed type 2 diabetes mellitus can be found in Scheme 1, where treatment combination may be initiated at an HbA1c level of over 10%.

A combination of 2 OAHs at a low dose may be and is usually initiated in the form of a combination of sulphonilurea and metformin. As stated in Scheme 1, an example of an initial treatment combination would be 1 mg of glimepiride plus 1000 mg of metformin, which reduces HbA1c to 2%, specifically from 9% to 7%. In patients with renal failure or congestive heart failure, metformin may be replaced with thiazolidinedione as a second choice. If it produces a hypoglycemic reaction, the dose of one of the drugs should be reduced or its administration terminated completely.[16] Diabetic patients with an HbA1c of less than 10% should be sufficiently treated with monotherapy, but nevertheless, treatment combination may be administered if necessary before reaching the maximum dose. If a combination of 2 OAHs is still ineffective, we may add the use of a third drug, usually thiazolidinedione, or insulin. The addition of thiazolidinediones delays the administration of insulin, but its effect varies and is generally slower. In addition, liver enzyme monitoring is required.[16] Administration of insulin is more reliable and more powerful. However, it is generally not preferred by patients. The type of insulin recommended is NPH, or moderate acting insulin, administered at an initial dose of 10 units at night before bed, and gradually increased until the fasting plasma glu-

cose is under control.[16] In the United States, sulphonilurea is chosen as a formality, and the recognized drug is glimepiride, even though other types of sulphonilurea are just as effective.

CONCLUSION

Treatment combination of two types of OAH with different mechanisms of action has been proven to be more significant in producing glycemic control compared to single drug administration.

Combination of two kinds of OAH, in addition to reducing side effects, can also delay the administration of insulin, which is generally disliked by patients. Sulphonilurea and metformin are the most common drugs to be combined, but other combinations can also produce equally satisfactory results. Even though it is able to reduce HbA1c, ombination of sulphonilurea and troglitazone cannot produce the expected euglycemic effect.

Patients who failed to reach the euglycemic control level with a combination of 2 kinds of OAH are recommended for treatment with moderate-acting insulin at night as an additional treatment, with a dose titrated to reach the euglycemic control level. Patients receiving a single drug who did not reach the euglycemic control level may be initiated on treatment combination before reaching the maximum dose, since the maximum dose produces more side effects.

REFERENCES

1. Chiu KC, Permutt MA. Genetic factors in the pathogenesis of NIDDM. In: Textbook of diabetes Pickup J,William G, editors. 1st ed. Massachussets USA: Blackwell Science ltd.; 1997. p.81.1-81.10.
2. Kruszynska YT. Metabolic disturbances in diabetes mellitus. In: Textbook of diabetes. Pickup J,William G, editors. 1st ed. Massachussets USA: Blackwell Science ltd.; 1997. p.29.1-29.5.
3. Consoli A. Role of liver in pathofisiology of NIDDM. J Diab Care.1992;15:430-41.
4. DeFronzo RA, Bonadonna RC, Ferranini E. Pathogenesis of NIDDM. J Diab Care 1992:15:318-68.
5. Sidartawan Soegondo: Penatalaksanaan diabetes melitus tipe 2 Naskah lengkap Simposium Free radicals in Diabetes and their interaction with sulphonylureas; 2001 Maret 24: Jakarta, Indonesia. Diamicron Scientific Collection; 2000. p.1-9.
6. Riddle M. Combining sulfonylureas and other oral agents. The Am J of Med. Proceedings of a symposium. 2000;108 Suppl 6A:15S-22S.
7. Askandar TJ. Novel OHA: A Prandial glucose regulator (Introduction with repaglinide). In: Adam JMF, Sanusi H, Aman M, editors. Naskah lengkap Simposium Diabetes mellitus New aproach in the treatment of type 2 diabetes; 2000 Okt 21-22; Makassar. Indonesia. Jakarta. Perkeni cabang Makassar; 2000. p.13-8.
8. Harrower ADB. Comparison of efficacy, secondary failure rate and complications of sulfonylureas. J Diab Comp 1994:8:201-13.
9. Kabayoshi M.Glimepiride : An oral antidiabetic agent. In: Turtle JR., Kaneko T, Osato S, editors. Diabetes in the millennium. The Endocrinol and Diabet Research Foundation of The University of Sydney 2000:203-6.
10. Chow CC. Repaglinide for prandial glucose regulation. Med prog 2000:27:37- 40.
11. Horton ES, Clinkingbeard C, Gatlin M Foley J, Mallow S, Shen S. Nateglinide alone and in combination with metformin improves glycaemic control by reducing mealtime glucose levels in type 2 diabetes. Diab Care 2000;23:1660-5.
12. Dunn CJ,Faulds D. Nateglinide. Drugs Adis Internqational Limited, Auckland. Newzealand 2000;60(3):607-15.
13. Stocks AE . Metformin. In: Turtle JR., Kaneko T, Osato S, editors. Diabetes in the millennium. The Endocrinol and Diabet Research Foundation of The University of Sydney 2000:207-11.
14. PI Sunyer FX. Acarbose. In: Turtle JR., Kaneko T, Osato S, editors. Diabetes in the millennium. The Endocrinol and Diabet Research Foundation of The University of Sydney 2000:213-7.
15. Kikuchi M. New antidiabetic drugs: Rapid onset and short duration insulin secretagogues and new insulinsensitisers acarbose. In: Turtle JR., Kaneko T, Osato S, editors. Diabetes in the millennium. The Endocrinol and Diabet Research Foundation of The University of Sydney 2000:239-2349.
16. Riddle M. Combining sulfonylureas and other oral agents. The Am J of Med. Proceedings of a symposium 2000;108 Suppl 6A:15S-22S.
17. ClarkJr CM. Oral therapy in type 2 diabetes: Pharmacological properties and clinical use of currently available agents. Diabetes Spectrum 1998:11:211-21.
18. DeFronzo RA, Goodman AM. The metformin investigator group: Efficacy of metformin in patients with NIDDM. N Engl J Med 1995:333:541-9.
19. Bayractar M, Van Thiel DH., Adalar N. A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients. Diabetes care 1996;19:252-4.
20. Marbury T, Huang WC, Strange P, Lebovitz H. Repaglinide versus gliburide: A one year comparison trial. Diabet care & Clin Pract 1999;434:155-6.
21. Balfour JA, Tavish DM. Acarbose: An update of its farmacology and therapeutic use in diabetes mellitus. Drugs Adis International Limited, Auckland, Newzealand 1993:46:1025-54.
22. Bayer. Anti diabetic: Glucobay (acarbose). April 1991:25-30.
23. Bell DSH. Converting patientss with type 2 diabetes from insulin requiring to non-insulin-requiring.Clin Diab 1997:5:205-7.
24. Wolffenbuttel HR, Gomist R, Squatrito S, Jones NP, Patwardhan N: Addition of lowdose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. British Diabetic Association. Diabetic Medicine 2000;17:40-7.
25. Moses R, Slobodniiuk R, Boyages S, Colagiuri S, et al. Additionall treatment eith repaglinide provides significant improvemnet in glycaemic control in NIDDM patientss poorly controlled on metformin. Diabetologia 1997:40 Suppl 1:A322.
26. Raskin P,Kennedy F,Woo V, et al. The therapeuticeffect of Repaglinide combained with troglitazone in subjects with type 2 diabetes. Diabetologia 1999;42:342-5.