Efficacy and safety of adding single dose insulin glargine in patients with type 2 diabetes uncontrolled by oral hypoglycemic drugs

***Dr.Ali Saad Al-Deen Abdul Razzaq Al-hilly(CABM,FICMS)**

الخلاصة : أستهدفت الدراسة الوقوف على فعالية وسلامة أضافة علاج الانسولين طويل الامد (كلارجين) لدى مرضى السكري من النوع الثاني غير المسيطر عليه بالادوية الفموية المخفضة للسكري .كشفت الدراسة ان اضافة جرعة واحدة من علاج الانسولين طويل الامد كلارجين الى الادوية الفموية الاخرى المخفضة للسكري ذو فعالية وأمان معتبرين في السيطرة على السكري من النوع الثاني.

Summary:

BACKGROUND:

The addition of the long acting insulin glargine (Lantus) to the regimen of multiple oral hypoglycemic drugs in patients with uncontrolled type 2 diabetes mellitus has long been studied in terms of efficacy (e.g. HbA1c reduction) and safety (e.g.incidence of hypoglycemia).

OBJECTIVES:

The aim of this study was to assess 1) effectiveness in controlling hyperglycemia 2) safety in terms of the incidence of hypoglycemia, after the addition of a single dose of insulin glargine to the previous regimen of oral hypoglycemic drugs in patients with uncontrolled type 2 diabetes.

PATIENTS AND METHODS:

200 patients with long standing (5-10 years) type 2 diabetes mellitus uncontrolled by multiple oral hypoglycemic drugs (HbA1c 9.5-13%) attending the diabetes center in Diwaniya, were selected to add a single titrated dose of insulin Glargine to their oral regimen and followed for 6 months to evaluate their glycemic control (as defined by HbA1c and FPG) and safety regarding the incidence of moderate and severe hypoglycemia.

RESULTS:

After 6 months, ,109 patients Of total 200 patients (54.5%) achieved both targets, HbA1c reduction (< 7 %) and fasting plasma glucose (< 130mg/dl), among them only 3 patients (2.7%) developed severe hypoglycemia and 17 patients (15.5%) developed mild to moderate hypoglycemia.64 patients (32%) achieved HbA1c between (7 - 7.5%) ,among them only 8 patients(12.5%) developed mild hypoglycemia. of the total 200 patients ,20 patients (10%) had their HbA1c between (7.5 – 8%) with only 2 patients among them (10%) had mild hypoglycemia. only 7 patients of the total 200 (3.5%)had HbA1c > 8% without hypoglycemia.

* Chief assistant of diabetes center in Al-Diwaniya teaching hospital

Abstract:

Unfortunately, a Significant number of type 2 diabetic patients on oral hypoglycemic agents are not achieving the desired and recommended target of glycemic control in terms of reduction of HbA1c and fasting plasma glucose, this is largely because most of them are reluctant to use insulin injections for many reasons, mainly the painful injection, fear of hypoglycemia or inability to adapt to a complex regimen of multiple insulin injections. it has been recommended by many diabetes associations (the American diabetes association(ADA) and the European association for the study of diabetes(EASD)), in their algorithm of management of hyperglycemia in patients with uncontrolled diabetes (HbA1c > 7 %) to add a basal (long acting) insulin to their oral drug regimen as a more simple initial step of adding insulin that is acceptable by most patients and capable of achieving target glycemic levels. insulin glargine is the preferred long acting insulin analogue for its pharmacodynamic properties (peakless action profile with low incidence of hypoglycemia and longer duration of action) , furthermore, its pen formulary makes it less painful than conventional human insulin syringe injections.

Introduction:

Diabetes is a chronic progressive disease of multifactorial etiology with well-known detrimental complications. the prevalence of diabetes has reached to about 400 million in 2014, The global prevalence of diabetes among adults above 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. 90 % of those are type 2 diabetic patients. Diabetes complications (neuropathy, retinopathy , nephropathy ,stroke and coronary heart disease) are major causes of mortality and morbidity all over the world ,this is mostly due to ineffective management of hyperglycemia and suboptimal lowering of glycemic variables to safe targets recommended by currently accepted guidelines that ensures significant reduction of life threatening diabetes complications .

In 2012, the American Diabetes Association(ADA) and Europian Association for the Study of Diabetes(EASD) recommended a consensus target HbA1c of < 7% and a fasting plasma glucose Of < 130 mg/dl without unacceptable hypoglycemia [1] . despite this guideline, only 37 % are achieving target A1C worldwide [3] .in most patients with type 2 diabetes oral antidiabetic agents are prescribed as an initial therapy. although many patients attain control, over the long term there is generally a requirement for intensified and multidrug regimens; ultimately, oral agents alone cannot maintain satisfactory control in many patients and therapy must be intensified by the addition of insulin [2]. Normally, pancreatic insulin secretion has two components: 1) basal(pre-prandial) secretion to suppress glucose production between meals and overnight ,and 2) bolus(postprandial) secretion in response to rising glucose levels after meals .therapy with basal insulin is a strategy that simulate the basal component of normal pancreatic insulin secretion that, if combined with oral therapy ,may help patients reach recommended glycemic goals. Basal insulins include NPH human insulin and two other insulin analogues (Glargine and Detemir) . basal insulins are mainly affecting fasting (or pre-meal) glucose levels, however, they can also lower postprandial glucose levels through overall

improvement in metabolic control [4]and together with oral agents can be a relatively simple and highly effective approach to insulin therapy [5] and can reduce hypoglycemia and weight gain observed in patients treated with insulin alone, and at the same time reduce the daily insulin doses required to reach optimal glycemic targets[6].

Patients and methods:

200 patients (119 female 81 male) attending the diabetes center in Diwaniya teaching hospital fulfilled the following criteria to be enrolled in this study (1) adult (age 45-65) with type 2 diabetes (more than 5 years duration) (2) taking maximum tolerated doses of at least two oral hypoglycemic drugs for at least 6 months (3) uncontrolled hyperglycemia (baseline HbA1c > 7% , in this study range was 9.5-13 %) and fasting plasma glucose > 130 mg/dl,in this study range was 190-320mg/dl). All patients continued their combinations of oral drugs (metformin and/or sulfonylurea and/or vildagliptin) with some modification of doses according to tolerance and assessment of risk of hypoglycemia (e.g. vulnerable elderly patients)

Insulin Glargine (Lantus;100 U /ml , sanofi-aventis) was added to the combined oral medications with initial dose (0.2mg/kg/day) given as a single daily dose either in the morning or at bed time according to patient life style then patients were followed weekly by fasting plasma glucose and insulin dose was adjusted(maximum 2-4 units increment/week) to reach the target fasting glucose of 130 mg /dl (maximum dose 30 units /day) .on each weekly visit patients were instructed to report any event of hypoglycemia (daytime or nocturnal) documented by laboratory or home glucometer.mild to moderate Hypoglycemia was defined as an event with or without symptoms consistent with hypoglycemia, not requiring the assistance of another person, and associated with BG concentration of <60 mg/dl . Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia, necessitating assistance, associated with a BG concentration of <40 mg/dl, or recovery after oral carbohydrate or intravenous glucose. HbA1c was measured at baseline and at 3 and 6 months after insulin initiation.

Discussion:

It has been estimated that, at the time of diagnosis of type 2 diabetes , about 50% of pancreatic β-cell function has been lost, with nearly 5% further loss of function expected every year thereafter (14-15). Therefore, type 2 diabetes is a chronic progressive disease characterized by worsening hyperglycemia and progressive deterioration in the function of pancreatic β-cells and loss of β-cell mass (16). Because of the progressive nature of the disease, an evolving treatment strategy is therefore necessary to maintain both fasting and postprandial glycemic control. Recently, an American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus recommended a logical target of A1C <7% for good glucose control in clinical practice (17). Insulin therapy is needed when oral hypoglycemic drugs combined with dietary restrictions and lifestyle modifications failed to provide acceptable glycemic control (18). One major lesson learned from the pioneer U.K. Prospective Diabetes Study (UKPDS) is the increasing requirement for multiple therapies in patients with type 2 diabetes to achieve acceptable blood glucose targets (19).

Complementing oral agents with insulin contributed to several beneficial metabolic effects, as recently reviewed (20). However, it is still controversial whether it is more beneficial to target

postprandial or fasting blood glucose concentrations, with basal insulin. Monnier et al. (21,22) provided data to explain the relative contribution of fasting and postprandial blood glucose to HbA1C in patients with mild-to-moderate hyperglycemia (A1C <7.5%) than in those with more severe hyperglycemia

Insulin therapy in type 2 diabetes can range from a single daily injection to basal-bolus replacement regimens with multiple daily injections. Insulin glargine is a long-acting insulin analog that is widely used in clinical practice for basal insulin replacement.

Type 2 diabetes is characterized by coexisting insulin deficiency and insulin resistance, with the resultant hyperglycemia leading to micro- and macro vascular complications. A large number of intervention trials demonstrated that improving glycemic control achieves considerable reductions of such complications (7-13). Numerous studies have investigated the clinical efficacy of insulin glargine in type 2 diabetes (24-26). Glargine has been found to effectively lower A1C, provide basal insulin replacement, and reduce the risk of hypoglycemia

Use of insulin glargine compared with NPH insulin is associated with less nocturnal hypoglycemia and lower post-prandial glucose levels. These advantages are attributed to peakless and longer duration of action of insulin glargine compared with NPH. Achievement of acceptable average glucose control requires titration of the insulin dose to attain FPG of 130mg/dl or less. These data advocate the use of insulin glargine instead of NPH in insulin combination regimens in type 2 diabetes.

Results:

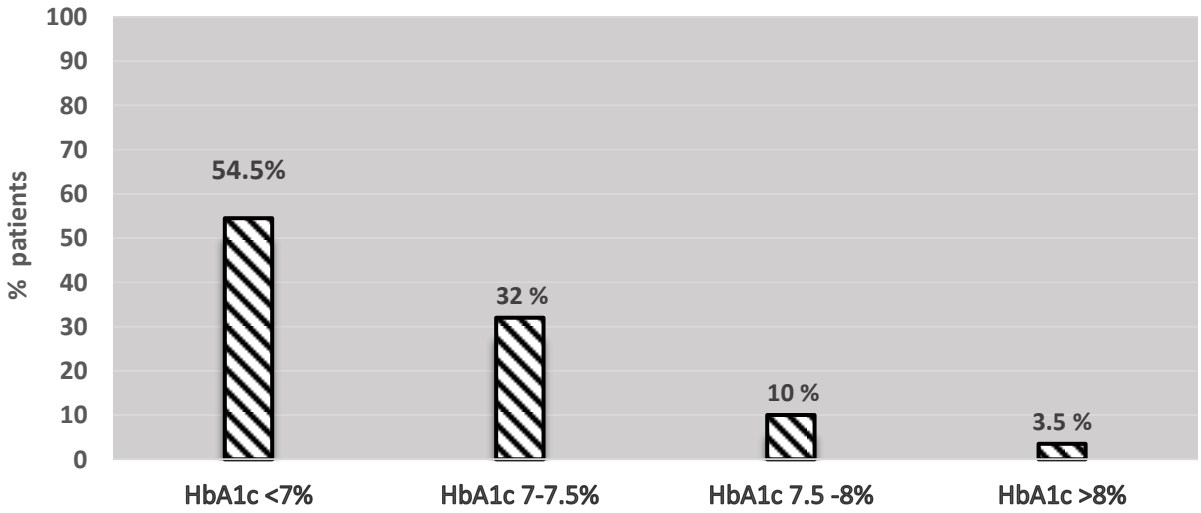

figure (1): distribution of patients according to their HbA1c % after 6 months of Glargine initiation

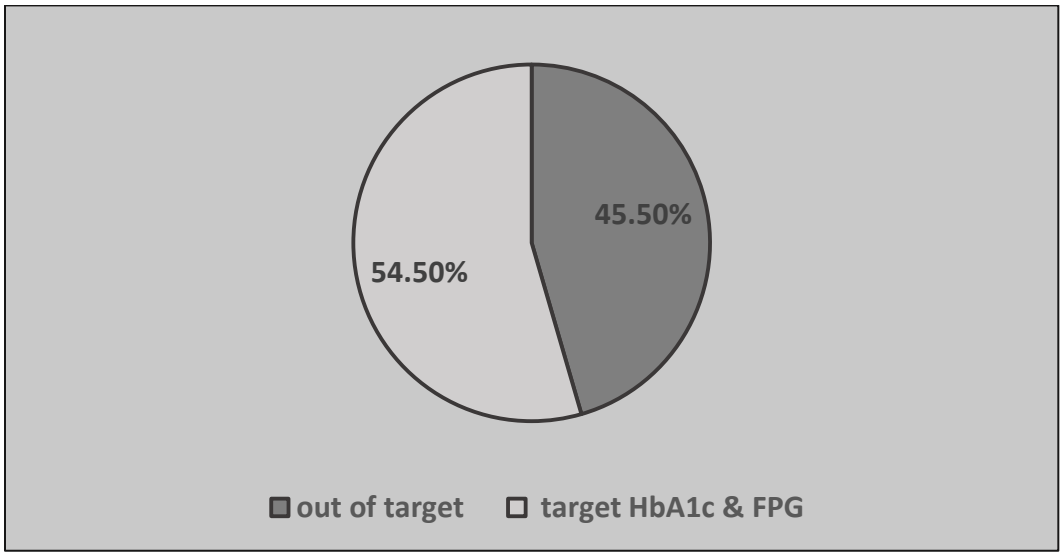

Figure (2) : Percentage of patients achieving target HbA1c (<7%) & FPG (<130mg/dl)

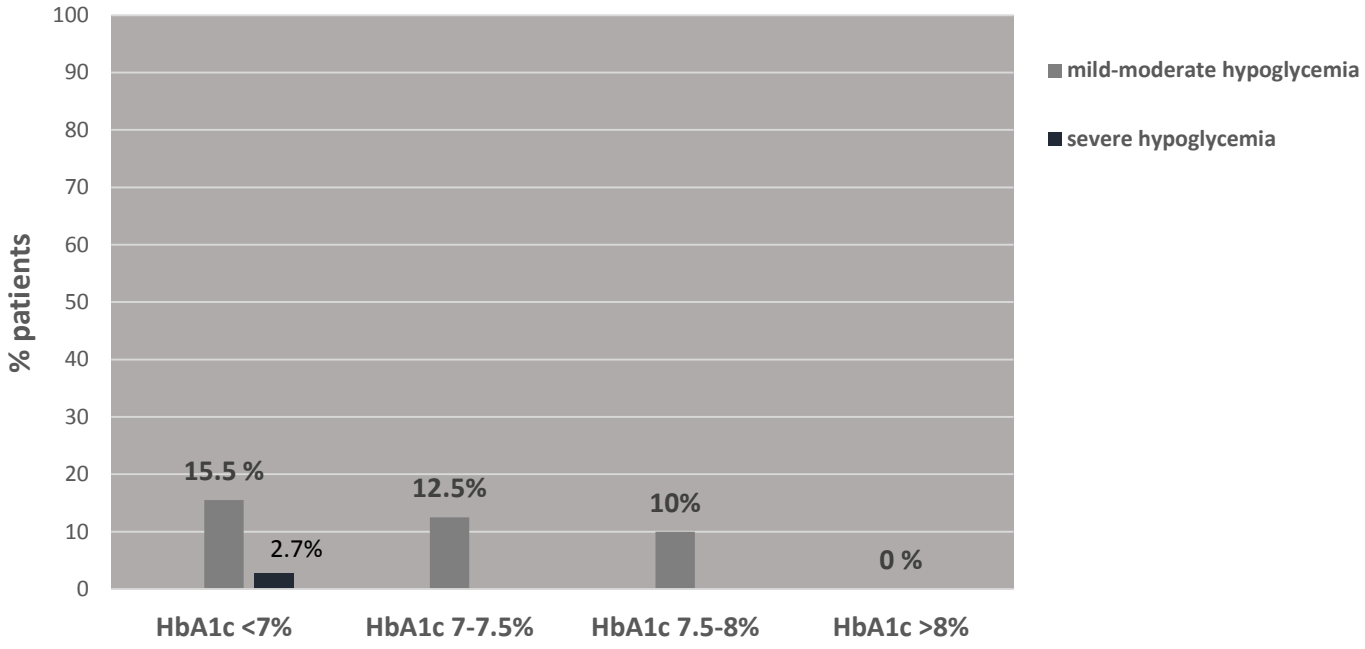

Figure (3): distribution of hypoglycemic events according to patient HbA1c

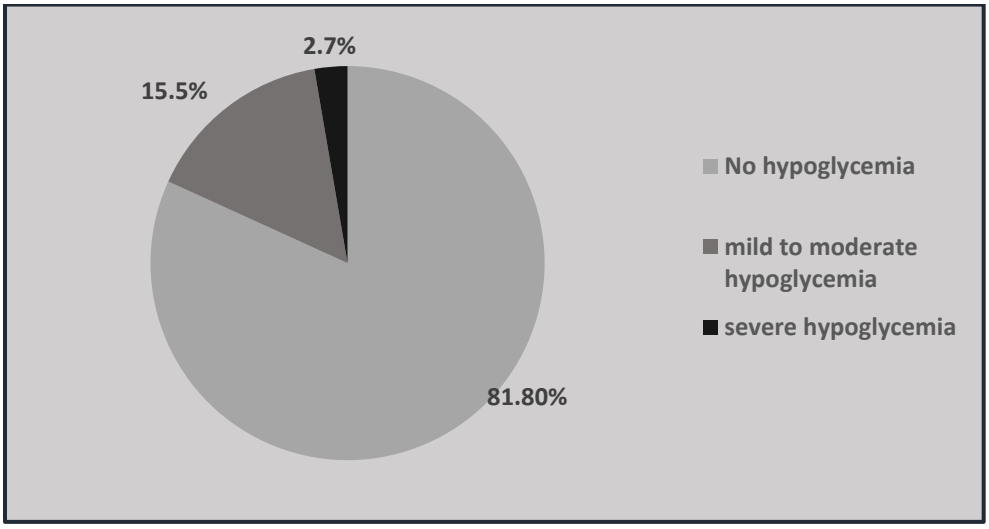

Figure (4): percentage of hypoglycemia among patients with target HbA1c & FPG

Conclusions and recommendations:

Among various approaches of intensification of treatment in patients with type 2 diabetes uncontrolled by multiple oral hypoglycemic drugs ,the addition of a single dose of the long acting insulin analogue Glargine to the oral regimen can effectively achieve recommended glycemic targets without incurring significant hypoglycemia .according to this study ,more than half of patients (54.5%) could achieve target glycemia utilizing such approach without significant risk of severe hypoglycemia (2.7%) . such single dose insulin regimen is highly recommended for its simplicity, flexibility, and tolerability by most patients who are reluctant to use conventional and more complicated multiple dose regimens of human insulin injections and will alleviate their fear of hypoglycemia. in other words, this approach would probably improve patient compliance to insulin therapy.

Further studies are needed to evaluate the long term efficacy and safety of such regimen and comparing its efficacy and safety with other insulin regimens.

References:

1. American Diabetes Association. Standards of medical care in diabetes-2006. Diabetes Care. 2006;29(Suppl 1):S4–S42.
2. American Association of Clinical Endocrinologists. The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: The AACE System of Intensive Diabetes Self-Management-2002 Update. Endocr Pract. 2002;8(suppl 1):40–82.
3. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA. 2004;291:335–342.
4. Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. Diabetes Care. 2000;23:1130–1136.
5. Vinik AI. Benefits of early initiation of insulin therapy to long-term goals in type 2 diabetes mellitus. Insulin. 2006;1:2–12.
6. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care. 2006;29:1963–1972.
7. Stratton M, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405– 412 .

8. Action to Control Cardiovascular Risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr, Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545– 2559.

9. ADVANCE Collaborative Group. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560– 2572.

10. Raz I, Wilson PW, Strojek K, Kowalska I, Bozikov V, Gitt AK, Jermendy G, Campaigne BN, Kerr L, Milicevic Z, Jacober SJ: Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009; 32: 381– 386.

11.Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD: VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med2009; 360: 129– 139.

12.Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P: Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials.Am Heart J 2006; 152: 27– 38.

13.Holman RR, Paul SK, Angelyn Bethel M, Matthews DR, Andrew H, Neil W: 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl pubJ Med 2008; 359: 1577– 1589 .

14. U.K. Prospective Diabetes Study Group U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249– 1258.

15.Holman RR: Assessing the potential for alpha-glucosidase inhibitors in prediabetic states. Diabetes Res Clin Pract 1998; 40 (Suppl. 1): S21– S25.

16. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC: Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52: 102– 110.

17. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; 29: 1963– 1972.

18. Brown AF, Gregg EW, Stevens MR, Karter AJ, Weinberger M, Safford MM, Gary TL, Caputo DA, Waitzfelder B, Kim C, Beckles GL: Race, ethnicity, socioeconomic position, and quality of care for adults with diabetes enrolled

in managed care: the Translating Research Into Action for Diabetes (TRIAD) study.Diabetes Care 2005; 28: 2864–2870.

19. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005– 2012.

20. Massi-Benedetti M, Orsini-Federici M: Treatment of type 2 diabetes with combined therapy: what are the pros and cons?. Diabetes Care 2008; 31 (Suppl. 2): S131– S135.

21. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; 26: 881– 885.

22. Monnier L, Colette C, Dunseath GJ, Owens DR: The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007; 30: 263– 269.

23. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T: Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008; 371: 1073– 1084.

24. Riddle MC, Rosenstock J, Gerich J Insulin Glargine 4002 Study Investigators The treat to target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients Diabetes Care 2003; 26: 3080–3086.

25. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005; 28: 254–259.

26. Fritsche A, Schweitzer MA, Häring HU: Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003; 138: 952–959.