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KEYNOTE ADDRESS

- The Role of Exenatide in Managing Cardiovascular Risks and Complications in Patients with Type 2 Diabetes

AIM OF PRESENTATION

- This presentation is based on a systematic review which examines the role of exenatide twice daily (BID) in managing cardiovascular risks and complications in patients with type 2 diabetes.

INTRODUCTION

- Type 2 diabetes is a progressive metabolic disorder of multiple aetiology
- It is characterised by defects in insulin secretion and/or insulin action in peripheral tissues leading to chronic hyperglycaemia [1].
- Patients with type 2 diabetes are at greater risk of developing cardiovascular disease (CVD).

INTRODUCTION CONTD

- According to Saraiva and Sposito [2];
- about 68% of people over 65 yrs of age with diabetes die of some form of cardiovascualr disease
- CVD deaths amongst adults with diabetes are 2 to 4 times higher than those without diabetes.

INTRODUCTION CONTD

- Some observational studies have demonstrated that a higher glycated haemoglobin (HbA1c) level was associated with increased risks of cardiovascular diseases and deaths.
- However, the underlying mechanisms remain complex [3,4].
- The progressive nature of type 2 diabetes despite the use of diet, physical activity and current therapies such as metformin, sulfonylurea and insulin may explain why therapeutic requirements tend to increase with time [1,5,6].

INTRODUCTION CONTD

- The addition of sulfonylurea and thiazolidinedione as treatment for diabetes are useful alternatives
- However, these may have their limitations including;
- The risk of hypoglycaemia
- Potential for weight gain and oedema
- Potential to reduce patient compliance [1,5].
- Based on the above, new therapies which do not have the usual side effects of the current therapies have to be developed.

INTRODUCTION CONTD

- The NICE guideline [7] for blood glucose lowering therapy in adults with type 2 diabetes include the use of metformin alone, dual therapy and triple therapy (such as metformin, a Dipeptidyl peptidase – 4 – inhibitor and sulfonylurea).
- If triple therapy is not effective, not tolerated or contraindicated;
- consider combination therapy with metformin, a sulfonylurea and a Glucagon –like peptide –1 (GLP – 1) mimetic.

INTRODUCTION CONTD

- To qualify for this treatment, patients should have;
- body mass index (BMI) of $\geq 35 kg/m^2$
- have a lower BMI than $35 kg/m^2$ and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity related co-morbidities.

INTRODUCTION CONTD

- According to McCormack [8], human GLP –1 is produced by L–cells of the intestinal mucosa and is an incretin.
- GLP–1 is a gastrointestinal hormone responsible for the enhanced secretion of insulin from the beta cells of the pancreas in response to food intake [9,10,11].

INTRODUCTION CONTD

- However, in patients with type 2 diabetes, the incretin effect is significantly impaired due to reduced production of GLP – 1, metablolism and/or impairment of their actions [12].
- The incretin effect is the difference in insulin secretion from an oral glucose load compared with intravenous glucose administration
- It results from the observation that intrajejunal glucose enhances greater insulin release than intravenous glucose administration [2,13,14].

INTRODUCTION CONTD

- GLP –1 receptor agonists such as exenatide significantly decrease glycated haemoglobin via;
  - suppressing glucagon production
  - delaying gastric emptying
  - reducing appetite and food intake by increasing satiety [9].

INTRODUCTION CONTD

- Exenatide is a 39 – amino acid peptide and is an incretin mimetic which was the first of the new incretin mimetic class of antihyperglycaemic agents to be marketed in the US and European Union [8,10].
- Exenatide is a short acting agent which can be administered subcutaneously twice daily (exenatide BID) although the extended release formulation can be administered once weekly (exenatide QW) [8].

METHOD

- The literature search included the following;
- a general scoping of the data bases which included;
- EBSCO host, encompassing Academic search premier, Medline, Psychology and Behavioural sciences collection, PSYCINFO, SPORTDISCUSS and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus.

METHOD CONTD

- However, the reviews found were either;
  - more than 5 years old
  - were narrative reviews
  - included liraglutide
  - were studies which were not randomised
- The current systematic review is based only on randomised controlled studies.

METHOD CONTD

- The search strategy relied on published guidelines for reviews [15,16] and was based on the PICO framework;
  - Population (P)
  - Interventions (I)
  - Comparative interventions (C)
  - Outcomes (O)
- The ‘Boolean’ search strategy allowing the combination of search terms.

TABLE 1: LITERATURE SEARCH STRATEGY

Database	Dates covered	Date searched	Search Terms	Hits
EBSCO Host	2010 – 2016	20.03.15	Exenatide AND Diabetes OR Glycaemic control	19,065
EBSCO Host	2010 – 2016	20.03.15	GLP–1 AND Diabetes	7,841
EBSCO Host	2010 – 2016	20.03.15	GLP–1 AND Diabetes AND Microvacular Complications	92
EBSCO Host	2010 – 2016	20.03.15	GLP–1 AND Diabetes AND Macrovacular Complications	74
EBSCO Host	2010 – 2016	20.03.15	Exenatide AND Diabetes OR GLP – 1	10,643
EBSCO Host	2010 – 2016	20.03.15	Type 2 Diabetes AND Exenatide	1,695
EBSCO Host	2010 – 2016	20.03.15	Type 2 Diabetes AND Exenatide twice daily	289
EBSCO Host	2010 – 2016	20.03.15	Type 2 Diabetes AND Exenatide twice daily AND Control	169

INCLUSION AND EXCLUSION CRITERIA

- Studies included were those written in English and published between 2010 and 2016 only.
- In addition, only randomised controlled studies were selected for review.
- Studies which did not meet the inclusion criteria outlined above were excluded from the review.
- The original hits were filtered and narrowed down using the above criteria.

QUALITY ASSURANCE

- This was based on the Scottish Intercollegiate Guidelines Network (SIGN) checklist for critical appraisal (Scottish Intercollegiate Guidelines Network (SIGN), [17] and my experience as a researcher.

DATA ANALYSIS

- On the basis of the inclusion and exclusion criteria, 19,065 articles including full articles and abstracts were initially found following a search of the databases (Table 1).
- However, based on the use of various search terms, this was significantly narrowed to smaller numbers.
- Of these, 11 articles which met the requirements for selection were included in the review (Table 2).

RESULTS

- All the eleven studies [18,19,20,21,22,23,24,25,26,27,28] (Table 2) for this review were multicentre and randomised controlled studies involving patients with type 2 diabetes.
- While seven of the studies [18,20,21,22,24,26,27] were conducted in at least 2 countries, the remaining 4 [19,23,25,28] were conducted in Italy, Japan, the US and Germany respectively.

RESULTS CONTD

- However, all eleven studies had background treatment in addition to the intervention treatments except the study by Gastaldelli et al [18].

- The background treatments included metformin and/or insulin glargine, pioglitazone, diet and exercise, and thiazolidinedione. Other background treatments were sulfonylurea and/or biguanide, thiazolidinedione and/or metformin.

RESULTS CONTD.

- The sample size of the studies ranged from 54 to 1,019 while the length of study ranged from 12 weeks to 4½ years.
- The duration of diabetes of the patients in the studies ranged from 1±2 to 12±7 years (Mean ± SD).

EXENATIDE TWICE DAILY VERSUS PLACEBO

- Exenatide twice daily were compared to placebo in seven of the 11 studies [18,19,20,21,22,23,24] (Table 2).
- Participants in the exenatide groups with metformin as one of the background treatments showed statistically significant decrease in body weight in five of the studies [19,20,21,22,23] compared to placebo group.
- However, mean reductions in body weight were not statistically significant between exenatide and placebo groups in the studies by Gastaldelli et al [18] and Liutkus et al [24].

EXENATIDE TWICE DAILY VERSUS PLACEBO

- The exenatide group in all the seven studies showed statistically significant decrease in HbA1c compared with the placebo group except for one study [22], where HbA1c reduction was not significantly different between the two groups (P=0.26).
- There were no significant differences in lipid profile between the exenatide groups and the placebo group [19,21,23,24] except with respect to HDL cholesterol in the study by Kadowaki et al [23]

EXENATIDE TWICE DAILY VERSUS PLACEBO CONTD.

- The Kadowaki et al [23] study showed that significant reduction in HDL cholesterol was statistically greater in both exenatide gps compared to placebo although no statistically significant difference was observed in total cholesterol, LDL-cholesterol and triglycerides.
- However, systolic and diastolic BP decreased significantly in the exenatide group compared to placebo group in two studies [19,21].
- In another study [24], diastolic pressure was significantly reduced in both treatment gps, while systolic blood pressure remained relatively unchanged from baseline values.

EXENATIDE TWICE DAILY VERSUS OTHER CONTROLS

- While one of the remaining 4 studies had placebo + lifestyle modification as control [25], the other 3 studies were not placebo controlled [26,27,28].
- The interventions included;
- Exenatide + lifestyle modification versus placebo + lifestyle modification with metformin and/or sulfonylurea as background treatment [25]
- Exenatide versus Glimepiride with metformin as background treatment [26,27]
- Exenatide versus premixd insulin aspart with metformin as background treatment [28].

EXENATIDE TWICE DAILY VERSUS OTHER CONTROLS

- In all the 4 studies [25,26,27,28] (Table 2);
- There were significantly better clinical outcomes in the exenatide groups compared with Glimepiride, premixed insulin aspart, placebo plus lifestyle modification programme
- These were based on the specific outcomes measured by each study including; body weight, blood pressure, lipid profile and glycaemic control.

EXENATIDE TWICE DAILY VERSUS OTHER CONTROLS

- With respect to HbA1c targets (<7% and <6.5%) exenatide twice daily was non inferior compared to premixed insulin aspart [28].
- In addition, there were significant differences in favour of the exenatide groups compared with the glimepiride group with respect to HbA1c < 7% (P<0.0001) and HbA1c <6.5% (P=0.0001) [27].
- The percentage of hypoglycaemia in the exenatide group was significantly (P<0.0001) lower than the glimepiride group [26].

EXENATIDE TWICE DAILY VERSUS OTHER CONTROLS

- When compared with the placebo plus lifestyle, the exenatide plus lifestyle groups had significantly more participants who had HbA1c ≤6.5% (P=0.001) [25].
- The study by Simo et al [26] showed that a statistically significant proportion of exenatide treated patients achieved the HDL-cholesterol goal than glimepiride treated patients at 36 months (P=0.21).
- In addition, systolic blood pressure (BP) [25,26,27] and diastolic BP [25,26] descreased significantly in the exenatide groups compared with controls.

TABLE 2: SUMMARY OF

Citation	Length of Study	Study Type	Sample Size	Age (Years)	Diabetes duration (Yrs)	Background treatment	Intervention	Glycaemic Control	Lipid Profile	Blood pressure and Heart rate	Outcomes/body weight
Gastaldelli et al [18]	24 weeks	Randomised Controlled Study	79	Exenatide (10 µg) 59±2 Exenatide (5 µg) 57±2 Placebo 54±2	2±3 (Exenatide 5µg) 2±3 (Exenatide 10 µg) 1±2 (Placebo)	–	Exenatide twice daily versus Placebo	Compared to placebo, 24 wks of daily high or low dose exenatide treatment significantly reduced HbA1c (P<0.01) and fasting plasma glucose (P<0.05)	–	–	There were no differences in wt. changes between the two exenatide and placebo groups
Derosa et al [19]	4 years	Randomised Controlled Study	174	57.1±7.6	7.8±3.2	Metformin Diet and exercise advise	Exenatide twice daily versus Placebo	Exenatide+ metformin were better than placebo+ metformin in decreasing HbA1c at 12months (P<0.05). Similar trend was recorded for fasting blood glucose.	No variation in lipd profile were observed in either of the 2 gps.	Systolic and diastolic BP were not changed by placebo+ metformin, but decreased by treatment with exenatide+ metformin at 12 months compared with point of randomisation (P<0.05)	Body mass and BMI obtained after 9months and 12months of exenatide+ metformin were lower than the ones obtained for placebo+ metformin gp (P<0.05 and P<0.01 respectively)

Rosenstock et al [20]	**30 weeks**	**Randomised Controlled Study**	**259**	**59 ±9 (Exenatide) 59 ±10 (Placebo)**	**12 ±7 (Exenatide) 12 ±7 (Placebo)**	**Insulin glargine, Metformin, Pioglitazone**	**Exenatide twice daily versus Placebo**	**Exenatide participants had greater HbA1C reductions compared with placebo participants at end point (P<0.001)**	**–**	**–**	**Exenatide participants lost more weight (P<0.05)**
Buse et al [21]	30 weeks	Randomised Controlled Study m	259	59 ±9 (Exenatide) 59 ±10 (Placebo)	12 ±7 (Exenatide) 12 ±7 (Placebo)	Insulin glargine with or without Metformin or Pioglitazone (or both agents)	Exenatide twice daily versus Placebo	HbA1c level decreased by 1.74% with exenatide and 1.04% with placebo (P<0.001). Proportion of participants who had minor hypoglycaemia were similar in both groups	Concentration of triglycerides, LDL, HDL did not differ between the groups	Systolic and diastolic pressures decreased (P<0.01 and P<0.001) respectively from basline with exenatide. Heart rate increased from baseline in the exenatide group	Wt. decreasd by 1.8kg with exenatide and increased by 1.0kg with placebo
Gill et al [22]	12 weeks	Randomised Controlled Study	54	Exenatide 57±11 Placebo 54±10	7 ±4 (Exenatide) 6 ±4 (Placebo)	Metformin, thiazolidinedione, Metformin+ thiazolidinedione.	Exenatide twice daily versus Placebo	HbA1c reduction was not significantly different between the 2 gps (P=0.26)	–	Differences in heart rate between the 2 gps was not significant (P=0.16). Exenatide therapy showed trends towards lower systolic BP, but similar diastolic BP between the gps.	There were significant differences (P<0.05) in body weight between exenatide and placebo gp

Kadowaki et al [23]	**24 weeks**	**Randomised Controlled Study**	**179**	**58 ± 10**	**12.2±6.3 (Exenatide 5µg)** **11.6±7.0 (Exenatide 10 µg)** **12.4±6.5 (Placebo)**	**Sulfonylurea,** **Sulfonylurea and biguanide, Sulfonylurea and thiazolidine derivative**	**Exenatide twice daily versus Placebo**	**The changes in HbA1c levels were significantly greater (P<0.001) in both exenatide gps than the placebo gp**	**The reduction in HDL cholesterol was statistically greater in both exenatide gps (5 µg, P=0.020 and 10 µg P=0.014) than placebo gp. No statistically significant differences were observed in total cholesterol, LDL cholesterol and triglycerides**	**–**	**Reduction in body weight were significantly greater (P=0.026) in exenatide 10 µg gp, than placebo gp.**
Liutkus et al [24]	26 weeks	Randomised Controlled Study	165	Exenatide (55±8) Placebo (54±9)	Exenatide (6.3±4.2) Placebo (6.4±4.6)	Thiazolidinedione, Metformin + Thiazolidinedione	Exenatide twice daily versus Placebo	Exenatide showed superiority with respect to change in HbA1c (P<0.001) and fasting serum glucose (P=0.009) compared with placebo	There were no significinant changes in fasting serum lipids between treatment gps	Diastolic pressure was significantly reduced in both treatment gps, while systolic BP remained relatively unchanged from baseline values.	Mean reductions in body weight were not significantly different between treatments at endpoint

Apovian et al [25]	**24 weeks**	**Randomised Controlled Study**	**194**	**54.8 ± 9.5**	**Exenatide (5.7±5.5)** **Placebo (5.3±5.1)**	**Metformin or Sulfonylurea or both**	**Exenatide twice daily + Lifestyle modification programme** **Placebo + Lifestyle modification programme**	**Significantly more participants treated with exenatide + lifestyle modification had HbA1c ≤6.5% at end point compared with placebo + lifestyle modification (P=0.001)**	**–**	**Exenatide + lifestyle modification was associated with significant decrease in systolic and diastolic BP at 24wks from baseline compared with placebo + lifestyle modification (P<0.001; P=0.04)**	**Exenatide + lifestyle modification had significantly more weight loss compared with placebo + lifestyle modification (P<0.01)**
Simo et al [26]	4½ years	Randomised Controlled Study	Exenatide (n=511) Glimepiride (n=508)	18 – 85	5.8±4.8 (Exenatide) 5.5±4.3 (Glimepiride)	Metformin	Exenatide twice daily versus Glimepiride	Symptomatic hypoglycaemia was reported during 1 yr of study treatment by 13.5% (exenatide gp) and 39.0% (glimepiride gp) (P<0.0001)	A sig. greater proportion of exenatide treated patients achieved the HDL-cholesterol goal than glimepiride treated patients at 36 months (P=0.21)	Between-group differences were significantly in favor of exenatide for systolic BP (P < 0.001), diastolic BP (P = 0.023)	Between-group differences were significantly in favor of exenatide for body weight (P < 0.0001), waist circumference (P < 0.001).

Gallwitz et al, [27]	**4½ years**	**Randomised Controlled Study**	**Exenatide = 490 Glimepiride= 487**	**18 - 85**	**5.8±4.8 (Exenatide) 5.5±4.3 (Glimepiride)**	**Metformin**	**Exenatide twice daily versus Glimepiride**	**44% in Exe natide gp and 31% in Glimepiride gp achieved HbA1c <7% (P<0.0001). 29% in exenatide gp and 18% in Glimepiride gp achieved HbA1c ≤6.5% (P=0.0001). Significantly fewer patients reported hyperglycaemia in exenatide gp compared with glimepiride gp (P<0.0001)**	**–**	**Systolic pressure decreased significantly in the exenatide gp (P=0.006) but not in the glimepiride gp (P=0.096). Heart rate increased in the exenatide gp.**	**Significant decrease (P<0.0001) in body weight in exenatide gp compared with glimepiride gp**
Gallwitz et al [28]	26 weeks	Randomised Controlled Study	354	57±10 (Exenatide) 57 ±9.9 (PIA)	5±4 (Exenatide) 5±5(PIA)	Metformin	Exenatide twice daily versus Premixed Insulin Aspart (PIA)	HbA1c targets <7% and <6.5% (Exenatide noninferior to PIA). Hypoglcaemic episodes with blood glucose ≤3.0mmols/L were less frequent with exenatide BID	–	–	Exenatide twice daily (Wt.loss =4.1±0.22kg) PIA (Wt.gain= 1.0±0.22kg) SEM (P<0.001)

DISCUSSION

- The exact mechanisms of control of cardiovascular risks and complications by exenatide are complex and still evolving [11,12].
- However, the findings of this review would suggest that the influence of exenatide in managing cardiovascular risks and complications may be through its effect in reducing glycated haemoglobin (HbA1c), reducing body weight and blood pressure.

DISCUSSION CONTD.

- This view is supported by previous reports which revealed that the potential effects of exenatide may be through glycaemic control based on the link between HbA1c and cardiovascular events and evidence that tight glycaemic control and/or decrease in HbA1c has been shown to reduce microvascular risks and complications [1,8,11].

DISCUSSION CONTD.

- Another possible mechanism of the effect of exenatide on cardiovascular risks and complications may be its impact on body weight.
- Based on the results of the studies reviewed, nine of the eleven studies showed significant decrease in body weight among participants in the exenatide group compared with placebo or control group.
- Only two studies [18,24] did not report statistically significant differences in body weight between exenatide group and control group.

DISCUSSION CONTD.

- While one of these studies had no background treatment [18], the other had thiazolidinedione, metformin plus thiazolidinedione [24].
- Therefore, it would appear that exenatide is more effective in reducing body weight in patients with type 2 diabetes when used in combination with metformin than when used alone or in combination with thiazolidinedione.

DISCUSSION CONTD.

- Increases in body weight and body mass index in patients with type 2 diabetes have been reported to increase the risk of cardiovascualr diseases whereas reduction in body weight increases insulin sensitivity and reduces blood pressure [11,31].
- Another mechanism of exenatide action on cardiovascular risks and complications may be its effect on the pathogenic link between type 2 diabetes and atherosclerosis [12].

DISCUSSION CONTD.

- The formation of advanced glycation endproducts (AGE) in patients with type 2 diabetes plays a key role in vascular damage and exenatide has been reported to ameliorate this deleterious effects of AGEs [12].
- According to Anagnostis et al [12], the main mechanism of the antihypertensive role of exenatide may be due to its effect on weight loss although the authors also alluded to the vasodilatory effects of GLP-1.

DISCUSSION CONTD.

- Although exenatide twice daily may improve blood pressure and certain lipid parameters, changes are often small and variable between studies [8,32].
- In the present review, the studies which looked at the effect of exenatide twice daily on lipid profile [19,21,23,24,25,26,27] did not find any significant difference between the exenatide group and the control group except for HDL – cholesterol [23,26].

CONCLUSION

- Based on the findings of this review, it would appear that exenatide twice daily may be useful in managing cardiovascular risks and complications by reducing body weight, HbA1c and blood pressure.
- In particular, the combination of exenatide with metformin was more effective in reducing body weight than using exenatide alone.

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