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REVIEW

Treatment of type 2 diabetes, lifestyle, GLP1 agonists and DPP4 inhibitors

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Abstract

In recent years the treatment focus for type 2 diabetes has shifted to prevention by lifestyle change and to more aggressive reduction of blood sugars during the early stage of treatment. Weight reduction is an important goal for many people with type 2 diabetes. Bariatric surgery is no longer considered a last resort treatment. Glucagon-like peptide-1 agonists given by injection are emerging as a useful treatment since they not only lower blood sugar but are associated with a modest weight reduction. The role of the oral dipeptidyl peptidase 4 inhibitors is emerging as second line treatment ahead of sulphonylureas due to a possible beneficial effect on the beta cell and weight neutrality. Drugs which inhibit glucose re-absorption in the kidney, sodium/glucose co-transport 2 inhibitors, may have a role in the treatment of diabetes. Insulin treatment still remains the cornerstone of treatment in many patients with type 2 diabetes.

Key words: Type 2 diabetes; Lifestyle modification; Dipeptidyl peptidase 4 inhibitors; Glucagon-like peptide-1 agonists; Insulin

Core tip: Treatment of diabetes is difficult. Initial success in achieving treatment goals is followed by deterioration and the necessity for additional treatments. Exciting new drugs with new modes of action, have stimulated diabetologists to strive for improved control in the knowledge that complications will be reduced or prevented. Obese patients, who loose weight on glucagon-like peptide-1 agonists are usually delighted with these drugs but for those who fail to loose weight changing to oral dipeptidyl peptidase-4 inhibitors would seem a good choice. sodium-glucose transporter-2 inhibitors have the added benefit of being effective even if blood sugar is near to target but uro-genital infection is a concern.

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INTRODUCTION

Readers interested in diabetes must be sick and tired reading that diabetes is a global problem of immense size and getting worse by the day with predictions that we will all have the disease one day! I exaggerate of course but it is sad to realise that although we know so much more about the condition we have made little progress in reducing or conquering the disease. A recent history of diabetes in the past 200 years by Polonsky[1] gives an excellent review of the history of discovery of so many mechanisms that are faulty in diabetes and the number of Nobel prize winners who have contributed to such wonderful success, yet more and more people are being diagnosed with the condition/disease and the consequences are immense in terms of suffering and financial cost. One should not forget that before the discovery of insulin 90 years ago

diabetes was a rapidly fatal disease and there was little interest in what we now term type 2 diabetes. Type 2 diabetes now makes up 90% of all diabetes. Insulin resistance rather than insulin deficiency is the major player in the vast majority of type 2 diabetes and type 2 diabetes can be reversed, at least in many patients, with exercise and weight reduction. This is not new information but was highlighted by Taylor's group in Newcastle in 2011[2] when they did a very simple experiment on patients who had diabetes, were obese and managed with tablets. They got 13 patients to do what was common practice and fashionable 40 years ago. They put the patients on an 800 kcal diet, a diet that has been proven beyond doubt to cause weight loss. Indeed there has never been a report of anyone who can maintain their weight on an 800 kcal diet. Compliance was checked by urinary ketones and weight loss. Eleven of the patients succeeded in finishing the eight week diet and lost as much weight as would be expected from bariatric surgery. Just like what happens following bariatric surgery in patients with type 2 diabetes, the diabetes disappeared and blood pressure and lipids improved. Nothing spectacular so far and the study would not have been worthy of reporting since all this is well known and has been done many times before, as Professor Yki-Jarvinen in her leading article in Diabetologia[3] wrote "the only problem is that in medical school and when I was training as an endocrinologist nobody told me how to get patients to follow such a diet". Only 10% of patients are able to follow dietary restriction advice and only the minority take the exercise treatment. Worse, of those who do succeed 90% relapse. Indeed this is why low calorie diets became unfashionable and large type 2 diabetic trials such as the Steino Hospital trial[4] did not include weight reduction as part of their protocol. The Newcastle group[2] converted an unoriginal and mundane study into a really exciting study by demonstrating that liver fat almost disappeared completely within a week and this was associated with a very large improvement in blood sugar and insulin resistance. The rapidity of improvement was interesting and the significance of the reduction of fat around the beta cell, a new finding of uncertain importance. However a plausible theory is that fat in the vicinity of the beta cell and in particular cholesterol, may be easily oxidised and the release of free radicals contributes to damage to the beta cell. In this regard a gene variant Ckal1, a gene associated with protein translation, has been shown to be very sensitive to oxidation and it is associated with a feeble insulin response[5]. Beta cells have the ability to regenerate and early and intensive reduction in blood sugar has been shown to improve beta cell function. Hyperglycaemia creates a vicious circle-the higher the blood sugar the greater the damage to the beta cell and the greater the damage to the beta cell the higher goes the sugar. Hence the drive to prevent hyperglycaemia by intervention in the pre-diabetes phase and to normalise blood sugar in the early stages of diabetes. The final result of the Newcastle group study that made me and many others sit up and take notice was the demonstration that the beta cell recovered, not partially but completely, and even the first phase insulin release returned to normal so the patients really did reverse their diabetes. This article was of such interest that it made headlines in daily newspapers around the world. Patients and their relatives, perhaps for the first time, really understood the damage diabetes does and gained new hope seeing a goal of reversal of diabetes and the possibility of discontinuation of diabetes medications. Beta trophin has been discovered-a hormone expressed mostly in liver and fat that stimulates beta cell proliferation, expands beta cell mass and improves glucose tolerance in a mouse model[6]. Perhaps an exciting new way to help to reverse diabetes in the future?

The July 2012 edition of the Lancet[7] carried on its cover "Physical inactivity: Worldwide", we estimated that physical inactivity causes 6%-10% of the major non-communicable diseases. Physical inactivity seems to have an effect similar to that of smoking or obesity. Min Lee *et al*[8] examined how much disease could be averted if inactivity were eliminated. Diabetes, as expected, is one of the major diseases the authors looked at. They concluded that not only did physical inactivity account for 6%-10% of the major non communicable diseases but this unhealthy behaviour causes 9% of premature mortality. There is good evidence to demonstrate that overweight or obese children who become obese as adults are at increased risk of diabetes whereas overweight or obese children who became non-obese by adulthood are not[9]. More importantly many studies have shown that educational interventions in physical activity have actually been successful and indeed more successful than interventions for obesity. Heath *et al*[10] in the same issue of the Lancet, examined interventions from around the world and demonstrate that the literature is convincing in demonstrating that behavioural and social approaches are effective. The improvements are seen among people of various ages and from different social groups, countries and communities. The authors make the point that although individuals need to be informed and motivated to adopt physical activity, the public health priority should be to ensure that environments are safe and supportive of health and wellbeing.

Since we know so much about the risk of developing diabetes, it should be possible to have treatment to prevent diabetes in many patients. The diabetes prevention program outcome study[11] has been recently published. This ongoing study demonstrated a clear reduction in diabetes incidence in participants randomly assigned to a lifestyle intervention or metformin during the intervention period. The authors end by stating that their data "support early and aggressive measures for long term prevention of diabetes in people at risk". Intensive lifestyle intervention has been shown to slow the decline in mobility in overweight adults with diabetes[12]. A disappointing result has recently come from the Look AHEAD study[13]. The study was designed to test the hypothesis that an intensive life style intervention for weight loss would decrease cardiovascular morbidity and

mortality in over weight patients with type 2 diabetes. More than 5000 patients took part in the study and the median follow-up of the study was for 9.5 years, weight loss was modest in the intervention group (6% *vs* 3.5% at the end of the study). Alas there was no reduction in the rate of cardiovascular events. The study results are perhaps not surprising in that significant weight reduction is unachievable in most patients but does suggest that we as physicians should accept that most patients are unable to loose weight and should not be made to feel guilty about this. On the other hand to continue to engage the patient in meticulous control of blood pressure, lipids and blood sugar, together with cessation of cigarette smoking, a healthy diet and exercise, are of proven benefit.

Casazza *et al*[14] have written an excellent article entitled "myths, presumptions and facts about obesity". The definition of a presumption was a belief in the absence of supporting scientific evidence; a Myth was defined as a belief persisting despite contradictory evidence. Facts were suppositions backed by sufficient evidence to consider them proven for practical purposes. The authors note that sometimes action is taken by policy makers in the absence of strong scientific evidence "This principle of action should not be mistaken as justification for drawing conclusions". The myths examined were: (1) that small sustained changes in energy intake or expenditure will produce large long term weight changes; (2) Setting realistic goals for weight loss is important otherwise patients will become frustrated and loose less weight; (3) Large rapid weight loss is associated with poor long term weight outcomes as compared with slow gradual weight loss; (4) It is important to assess the stage of diet readiness in order to help patients who request weight loss treatment; (5) Physical education courses in their present form play a part in reducing childhood obesity; (6) Breast feeding is protective against obesity; and (7) A bout of sexual activity burns 100-300 cal for each participant.

A stepwise approach to the management of diabetes has become a fashionable concept in recent years with many published paradigms of the steps which are variable and often contradictory or display so many different stairways that they become very confusing. The first step depends on getting the patient at the very beginning of their path, that is in the pre-diabetes stage but even then they may have already suffered from macrovascular and microvascular damage[15-18]. There is little dissention in advising the lifestyle changes but, should metformin also be used or should one wait and see the effect first of the lifestyle changes? Information on this point is available, for example in the trial by Snehalatha *et al*[19] 2009. There seemed to be no advantage to add metformin to life style changes so perhaps metformin should be reserved for those patients who are unable to adhere to life style changes?

Once diabetes has been diagnosed can one wait and see the result of life style changes or should one aggressively control blood sugar? High glucose is toxic to the beta cell. Exciting new information suggests that the beta cell may dedifferentiate under high glucose attack by causing reduction in a key transcription factor, Fox 01. This dedifferentiation results in the production of inactive proinsulin and an increase in glucagon[20]. Intensive insulin therapy at diagnosis of type 2 diabetes has been shown to reverse diabetes. Weng *et al*[21] studied 382 patients and had divided them into 3 groups. Continuous insulin infusion, multiple injections or oral agents were used to achieve rapid normalisation of hyperglycaemia. Treatment was stopped after normoglycemia was maintained for two weeks. After a year 51% and 44% of the insulin treated patients were in remission where as only 26% of the patients in the oral agent group had gone into remission. The evidence to support early and aggressive treatment for type 2 diabetes has not been widely accepted. The reasons are probably due to a shortage of personnel to manage patients. In my country there is a long waiting list to be seen in a diabetic clinic and general practitioners are usually unhappy about starting insulin. The better understanding of the beta cell pathology of diabetes should persuade physicians to adopt a more urgent approach to diabetes management in the future. A systematic review and meta-analysis on short term intensive insulin therapy in type 2 diabetes gives further support for the ability of this treatment to modify disease progression[22].

BARIATRIC SURGERY

Bariatric surgery for obese type 2 diabetes has been refined over the last few years. Laparoscopic surgery has made operation on morbidly obese patients who have diabetes, and indeed those who do not have diabetes, much safer and very often will reverse the diabetes. The operation has been shown to reduce cardiovascular risk. As with all operations the experience of the surgeon and indeed the surgical unit plays a very important part in outcome. A Cochrane review[23] in 2009 concluded that bariatric surgery is more effective than conventional treatment in achieving and in sustaining weight loss in people with obesity. Improvements in health related quality of life and obesity related co morbidities including type 2 diabetes, dyslipidaemia and sleep apnoea are further benefits. A very good review of the subject has recently been written by Dixon *et al*[24].

Mingrone *et al*[25] in 2012 published a single centre non-blinded randomised controlled trial to examine the difference in outcome between surgery as compared to usual medical therapy. Surgery was either gastric bypass or bilio-pancreatic diversion. At the end of 2 years HbA1c was 6.35% in the gastric bypass group and 4.95% in the bilio-pancreatic-diversion group as compared to 7.69% in the medically treated group. Diabetes remission had occurred in 75% of the gastric bypass group and 95% in the bilio-pancreatic diversion group. No patient in the medical group had reversed their diabetes. There were no deaths and almost no complications in the surgical group[25].

In the same edition of the journal Schauer *et al*[26] evaluated the efficacy of intensive medical therapy as compared to medical therapy plus Roux en Y gastric bypass or sleeve gastrectomy in 150 obese patients with uncontrolled type 2 diabetes. The primary end point was the proportion of patients with a glycated haemoglobin level of 6.0% or less, 12 mo after treatment. Twelve percent of the medical group, 42% in the gastric bypass group and 37% in the sleeve gastrectomy group achieved the primary end point. HbA1c was 7.5% in the medical group 6.4% in the gastric bypass group and 6.6% in the sleeve gastrectomy group. No deaths or life threatening complications occurred[26]. An editorial in the same edition by Zimmet *et al*[27] suggests that the bariatric surgery should not be seen as a last resort. More recently Arterburn *et al*[28] did a retrospective analysis to compare rates of diabetes remission, relapse and all cause mortality amongst severely obese adults with diabetes who underwent bariatric surgery *vs* non-surgical treated individuals. At 2 years the surgery subjects had significantly higher diabetes remission rates 73.7% compared to non surgical subjects with 6.9%. The surgical subjects also experienced lower relapse rates with no higher risk of death[28].

NEW INSULINS FOR TREATMENT OF TYPE 2 DIABETES

Many different regimes have been proposed and indeed are in use for the treatment of type 2 diabetes when life style and metformin have failed to control hyperglycaemia. A three year efficacy of complex insulins in type 2 diabetes demonstrated that the addition of a basal or prandial insulin based regimen to oral therapy had better diabetic control than those who added a biphasic insulin regimen[29]. My own feeling is that, as so many patients with type 2 diabetes don't increase their blood sugars overnight, attention should be paid to controlling the post evening meal rise in blood sugar so that the patient goes to bed with a normal blood sugar, long acting insulins being reserved for those patients in whom blood sugars rise overnight. To me it doesn't make sense to give a basal dose of a long acting insulin pre bed with the risk of overnight hypoglycaemia to a patient whose blood sugar has not been shown to rise overnight. Insulin degludec is almost identical to human insulin but with the last amino acid deleted from the B chain and addition of a glutamyl link from LysB29 to a hexadecanoic fatty acid[30]. Two phase 3 studies were reported recently[31,32]. In the first study type 1 diabetic patients (472 subjects) were subjected to insulin degludec and 157 to glargine insulin[31]. Although there was no difference in HbA1c at the end of the study and no difference in overall, confirmed hypoglycaemia; overnight hypoglycaemia was 25% less in the insulin degludec and of course nocturnal hypoglycaemia is what many patients fear most. The second study Garber *et al*[32] reported the effect of the new insulin in type 2 diabetic patients *vs* insulin glargine. Again after 1 year there was no difference between the 2 groups in HbA1c. Overall hypoglycaemia was a little less in the insulin degludec group and nocturnal hypoglycaemia was also a little lower (1.4 *vs* 1.8 episodes per patient-year exposure). The authors conclude that the newer basal insulins with lower hypoglycaemia events may allow more intensive blood sugar lowering treatment. From the results presented in their paper, insulin degludec does not seem to be the answer. An editorial by Tahrani *et al*[33] in the same edition, ends by saying that insulin degludec is not a revolution but an evolution of insulin therapy for patients with both type 1 and type 2 diabetes.

SODIUM GLUCOSE CO-TRANSPORT-2 INHIBITORS

Glycosuria occurs when the blood glucose reaches a threshold of about 10 mmol/L. However some people will excrete glucose at much lower levels of blood glucose (renal glycosuria). The discovery that glucose is transported across the proximal tubule membrane by sodium/glucose co-transport 2 (SGLT2) and that a naturally occurring polymorphism of the gene causes renal glycosuria, paved the way for the development of SGLT2 receptor inhibitors as a way of promoting renal glucose excretion and therefore calorie loss and reduction of blood sugar. Two drugs have undergone clinical trials dapaglifozin and canaglifozin and have been the subject of a meta analysis by Clar *et al*[34]. The drugs both result in blood glucose reduction of about 0.5%-1% with some weight loss. Urinary and genital infections were more common. Hypoglycaemia did not occur any more frequently that placebo. The results of the Cantata-SU trial have recently been published[35]. The trial was a 52 wk study in type 2 diabetes with patients who were inadequately controlled with metformin. Canagliflozin was compared to Glimepiride. 1452 patients were randomised in a phase 3 non-inferiority, double blind, randomised trial. Three hundred mg of Canagliflozin reduced HbA1c from a mean of 7.8% to 6.9% (mmol/L) a reduction of 0.9%. Hypoglycaemia was less common on Canagliflozin and there was a 4 kg reduction in weight with a small reduction in blood pressure. There was a 0.25 increase in LDL cholesterol but also a slight, 0.1% increase in HDL cholesterol and a very slight reduction in triglycerides also of 0.1%. Genital mycotic infections occurred in 8% in men and 14% in women on the 300 mg dose. The study suggests that the benefit of the drug is a useful reduction in HbA1c and weight reduction. The blood pressure reduction is also of benefit but the rise in LDL might be a worry and the mycotic genital infections and urinary tract infections might make the drug unacceptable to many patients who may have presented with these problems when first diagnosed. An editorial in the Lancet where the results were published is entitled "SGLT2 inhibitors for diabetes: turning symptoms into therapy" and makes the point that the place of this class of drugs in the treatment of type diabetes is still to be decided[36]. There has been concern about breast and bladder cancer as well

as long-term cardiovascular adverse effects also making surveillance mandatory. Another recently published study comparing canagliflozin with placebo and sitagliptin produced similar results[37]. A randomised, blinded, prospective Phase 111 study on dapagliflozin as monotherapy in drug naive Asian patients with type 2 diabetes found that with the 10 mg dose HbA1c had fallen from a mean of 8.26% to 7.15% as compared to a fall of only 0.29% for placebo(a difference of 0.82%) Genital infections occurred in 4.5% of patients and Urinary tract infections in 5.3%[38].

The role of these drugs in the treatment of type 2 diabetes is not clear at present but the lack of risk of hypoglycaemia and the weight reduction suggest that there is a place for them in certain patients who are inadequately controlled and in whom an extra 0.5% or more reduction in blood sugar would be of benefit in bringing the patient into the acceptable blood sugar range.

METFORMIN

The reason for metformin as first line pharmacological treatment is based on many studies suggesting that metformin is weight neutral or associated with very modest weight loss as compared with sulphonylureas which cause slight weight gain initially. Also, in experimental conditions reperfusion after myocardial infarction is reduced by sulphonylureas. As long ago as 1971 the University Group Diabetes Program[39] showed that tolbutamide, a first generation sulphonylurea, was associated with an increased cardiovascular risk in diabetes. The UKPDS trial[40] suggested that metformin has a protective effect on mortality. Roumie *et al*[41] examined the comparative effectiveness of sulphonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitius. This was a very large retrospective cohort study examining cardiovascular outcomes. The crude rates of composite outcome were 18.2 per 1000 person years in the sulphonylurea users and 10.4 per 1000 person years in the metformin group. A wonderful editorial in the same edition of the Annals of Internal Medicine by Nissen[42] entitled "Cardiovascular effects of Diabetes Drugs; Emerging from the dark ages", likens the dark ages after the fall of the Roman Empire to the time between the University Group Diabetes Program in 1972[39] which showed that treatment for diabetes with phenformin or tolbutamide was associated with increased cardiovascular risk, and 2012. The article explains why there is still uncertainty about the effect of sulphonylureas and cardiovascular events. Nissen[42] suggests that the study is hypothesis generating rather than definitive and that high quality evidence is still missing "Continued darkness is not an acceptable option" he concludes.

INCRETINS

It has been known for many years that intravenous glucose will not stimulate insulin secretion to the same extent as a similar glucose load given orally. It was discovered that hormones secreted from the intestine in response to a glucose load had the ability to release glucose from the pancreas. These hormones were called incretins and they are responsible for at least 50% of insulin secretion following a meal. In 1971 a peptide was isolated from the intestine which had the ability to inhibit gastric acid secretion and was therefore called gastric inhibitory polypeptide (GIP)[43]. GIP was later found to stimulate insulin secretion. What was very interesting was that GIP would only stimulate insulin secretion in the presence of high blood sugar. This finding has implications in treatment terms since drug that only works with high blood sugar would be much less likely to cause hypoglycaemia. Patients, their families and of course doctors and other health care professionals all fear hypoglycaemia. Garber[44] refers to the many hospital visits caused by hypoglycaemia and suggests that minimisation of hypoglycaemia should be a goal for treatment of type 2 diabetes. I would certainly agree. In a survey insulin accounted for 13.9% of overall admissions to hospital from adverse drug reactions and oral anti-diabetic drugs 10.7%[45].

Another incretin was discovered in 1985 and called glucagon-like peptide-1 (GLP-1)[46]. This hormone was also dependent on high blood sugar level for full action. Both GIP and GLP-1 act by binding to specific receptors and so release insulin. GLP-1 has another action, it inhibits gastric emptying and this has been of benefit in the treatment of diabetic patients because the feeling of satiety leads to weight reduction. Another beneficial effect of the reduction in rate of gastric emptying is to delay absorption of food, a mechanism which improves blood sugar excursion. GLP-1 also regulates appetite and food intake through its effect the hypothalamus. A recent review of the effects of GLP1 on appetite and body weight with a focus on the central nervous system has been published[47].

GLP-1 agonists have been shown to stimulate B cell growth in animals and cell cultures. In humans it is less clear if these drugs can improve insulin output by regenerating the B cell. It seems less likely that the dipeptidyl peptidase (DPP)-4 inhibitors could also have an effect on B-cell re-growth. However an abstract presented at the Annual American Diabetes Association meeting in 2010 suggested that linagliptin was able to restore beta cell function in human isolated islets[48]. Vildagliptin has also been shown to improve beta cell function and glucose tolerance but also to improve the extensive peri-insulitis found in the mouse model examined[49].

A very interesting effect of GLP-1 analogue therapy has been described in obese type 2 diabetic patients. The investigators found a reduction in inflammatory macrophages and a reduction in inflammatory cytokines together with an increase in the adipokine adiponectin. The researchers had previously described a case of psoriasis that was greatly improved by GLP-1 agonist therapy[50]. The new study does suggest an important beneficial effect of GLP-1 analogue therapy that needs further inves-

tigation[51]. A good review on the extrahepatic effects of GLP-1 receptor Agonists has just been published[52].

DEVELOPMENT OF GLP-1 FOR THE TREATMENT OF DIABETES

Exenatide is a GLP-1 receptor agonist. It is a 39 amino acid peptide produced in the saliva glands of the Gila monster lizard[53] it has 53% amino acid homology to full length GLP-1 and it binds with greater affinity than GLP-1 to the GLP-I receptor in GLP-1 receptor expressing cells[54]. DPP-4 cleaves peptides and is responsible for the rapid breakdown of GLP-1. DPP-4 does not denature exenatide because of the slight amino acid differences and in human studies the half life ranges from 3.3 to 4 h[55]. Exenatide (Eli Lilly) is now in clinical use in many countries for the treatment of diabetes. It must be given an hour before meals on a twice a day basis. Many trials have reported that the drugs cause about a 1% reduction in HbA1c and reduction in body weight of 5.3 kg at the end of 3 years of treatment[56]. The dropout rate is about 20%, many patients refusing treatment because of nausea.

EXENITIDE

Attempts have been made to prolong the action of exenatide using a polylactide glycolide microsphere suspension so that the drug can be given weekly. Kim *et al*[57], in a randomised placebo-controlled phase 2 study examined the effect of exenatide long acting release, a long acting release exenatide formulation, found that a weekly dose for 15 wk in patients with type Ⅱ diabetes resulted in a 1.4% reduction in HbA1c, suggesting that once a week formulation may be as good as, if not better than, twice daily injections of exenatide. In particular there were no dropouts in the trial due to adverse events. Liraglutide is a long acting GLP-1 analogue with attachment of a C-16 free fatty acid derivative. The free fatty acid derivative promotes non-covalent binding of liraglutide to albumen thereby increasing plasma half life. A recent study comparing liraglutide once a day with exenatide twice a day found that liraglutide improved HbA1c significantly more (-1.12% *viz* -0.79%) and was generally better tolerated[58]. The study has demonstrated that glycaemic improvement and weight reduction are independent of each other. This fits in with other studies which suggest that the weight loss is not, in itself, the cause of the improved blood sugar control[59].

In a recent paper Derosa *et al*[60] examined the effect of exenatide on beta cell function. The authors used the homeostasis model assessment beta cell function index as well as assessing pro-insulin and insulin with arginine stimulation under clamp conditions. The results suggested that beta cell function was improved by exenatide. However a caveat, HbA1c was significantly better after the 12 mo of exenatide as compared to placebo. It is well known that hyperglycaemia is toxic to the beta cell hence the improved glucose might have been responsible for the beta cell improvement rather than the drug itself. Bunck *et al*[61] showed similar results compared to glargine. In their study combined glucose and arginine stimulated C peptide secretion was 2.46 fold greater after 52 wk of exenatide treatment compared with insulin glargine treatment with a non significant (P = 0.55) 0.8% reduction in HbA1c as compared to a -0.7% reduction in the glargine group. Four weeks after cessation, the beta cell function returned to pre treatment levels.

Exenatide, was compared to glimepiride in patients who were not controlled on metformin alone[62]. About 1000 patients were divided into 2 groups and studied on average for 2 years although some went on for 42 mo. At the end of 3 mo both groups had decreased HbA1c from around 7.4% to 6.8% but by 36 mo the glimperamide group had gone back to a HbA1c of more than 7.3% whereas the exenatide group, although increasing their HbA1c slowly over the 3 years, was significantly lower at a level of just over 7.2%. Body weight fell in the exenatide group by 3.32 kg and rose in the glimperamide group by 1.15 kg. Systolic blood pressure (BP) decreased in the exenatide group by 1.9 mmHg with no change in the Glimpereride group. Less patients in the exenatide group experienced a hypoglycaemic episode. In the first 6 mo 49 patients in the exenatide group discontinued mostly due to gastrointestinal side effects as compared to 17 in the glimepiride group (P = 0.001) Buse *et al*[63] examined whether twice daily exenatide injections reduced HbA1c levels more than placebo in patients receiving Glargine insulin. HbA1c decreased by 1.74% in the exenatide group as compared to 1.04% in the placebo group over a 30 wk period. Hypoglycaemia was similar in the 2 groups and 13 treatment patients and 1 placebo recipient discontinued the study because of adverse events, nausea and vomiting being the main problems.

LIRAGLUTIDE

At the beginning of 2012 the FDA approved the marketing of extended release exenatide (Bydurion). The drug is given weekly by injection. Liraglutide is a human GLP-1 analog given by once daily injection with a good safety record and HbA1 lowering effect similar to the other GLP-1 agonists. A 2-year report on safety, tolerability and sustained weight loss over 5.2 years with once daily liraglutide has been published[64]. Two hundred and sixty eight of 398 people who entered the extension of the original 20 wk trial completed 2 years. Weight loss was 7.8 kg from screening and was maintained. There were improvements in BP and lipids. Patients with diabetes however were excluded from taking part in this trial. The Duration Trial 6[65] reported on a study comparing daily liraglutide to weekly extended release exenatide. This was a 26 wk trial with more than 400 patients in either arm. Liraglutide was associated with a greater change in HbA1c (-0.48% *viz* 1.28%). Nausea was more common in the liraglutide group (21% *viz* 9%) and also vomiting (11% *viz* 4%) 5% of patients allocated to liraglutide discontinued the treatment as compared to 3% allocated to exenatide because

of adverse events. The results suggest that the patient might be allowed to choose whether to have a drug which is injected daily but with no diluting procedure before the injection or a weekly injection with less blood sugar lowering effect but less side effects. Non-alcoholic steatosis has become a problem in type 2 diabetes. The LEAN study is currently examining whether liraglutide will improve non-alcoholic steatohepatitis outcome[66].

LIXISENATIDE

Lixinitide is another potent, selective, once daily GLP-1 agonist. A randomised placebo controlled double blind trial examined lixisentide daily injection in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without sulphonylureas[67]. This was a 24 wk study. These patients were not obese body Mass Index 25.3 kg/m^2. Eighty-two percent of patients reached and stayed on the maintenance dose of lixisenatide (20 μg once a day). There was a significant reduction in HbA1c compared to controls. The difference at the end of the trial was 0.88%. There was no significant change in weight compared to controls. The incidence of serious side effects were similar in both groups. Two patients in the lixisenatide group experienced cerebrovascular infarction. Forty-two percent of study drug patients experienced hypoglycaemia as compared to 24% on placebo. Fonseca *et al*[68] examined efficacy and safety of once daily lixisenatide at different doses. HbA1c was reduced by 0.66% compared to placebo. Postprandial and fasting blood sugars were significantly lower in the treatment group. In a study by Kapitza *et al*[69] lixisenatide once daily was compared to liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. This was only a 28 d study but the results showed that liraglutide controlled fasting blood glucose better than lixisenatide but postprandial blood sugar was better controlled by lixisenatide. A review discussing the place of this GLP-1 agonist as an add on therapy to basal insulin has recently been published[70].

TASPOGLUTIDE

Ipsen Roche had another GLP-1 analogue under review called taspoglutide. This is a GLP-1 analogue which has a prolonged action and is in phase Ⅱ trials. The drug has been shown to improve diabetes control and lowers body weight in subjects with diabetes. In a study involving once a week injections in 306 type 2 diabetic subjects who were already on Metformin, 8 wk treatment was associated with a reduction in HbA1c. The highest dose gave an HbA1c reduction of 0.9% and a weight reduction of 1.9 kg as compared to placebo. Nauck *et al*[71] report on a 24 wk study using a 10 mg or a 20 mg dose of Taspoglutide, comparing once a week dosing to daily glargine insulin. One thousand and forty-nine patients were randomised into 3 groups. Withdrawal rates were 21% for each of the Taspoglutide groups and 9% for the glargine group. HbA1c of < 53% was achieved in 39.47% and 32% receiving Taspoglutide 10 mg, 20 mg and HbA1c < 48 in 18%, 24%, and 14% of patients or glargine insulin respectively. Lower fasting blood sugars were achieved by glargine insulin. Serious hypersensitivity reactions occurred in 2 patients on Taspoglutide. However confirmed hypoglycaemia was less with the study drug (0.3%, 0.9% *viz* 3.1%) and weight loss was greater on Taspoglutide (-3.3 and -4.1 kg). Withdrawals due to adverse effects occurred in 9%, 13% on Taspoglutide and in 1% on the glargine insulin. An addendum to the paper states that Roche has now stopped the development of the drug. Ibsen is currently pursuing further investigations. Rosenstock *et al*[72] examined the fate of Taspoglutide once a week *vs* Exenatide for type 2 diabetes. The doses used were again 10 mg or 20 mg as compared to twice daily exenatide 10 μg. Reduction in HbA1c was -1.24 with 10 mg and -1.31 with the 20 mg as compared to exenatide from a starting HbA1c of 8.1%. Withdrawals were higher in the study drug patients and the authors conclude that even though Taspoglutide caused lower blood sugars the level of side effects was unacceptable.

Albiglutide is a long acting subcutaneous albumen-based fusion of GLP-1[73]. In February 2009 Glaxo SmithKline (GSK) began phase 3 studies in type Ⅱ diabetes. Albiglutide is a GLP-1 mimetic generated by genetic fusion of a DPP-4-resistant GLP-1 dimer to human albumin[74]. The formulation was originally developed by Human Genome Sciences (HGS) and named Albugon, GSK having bought the drug in 2004 for all human therapeutic and prophylactic applications of Albiglutide. In 1999 Centeon (now Aventis Berring) granted Principia (now HGS) world wide rights to its recombinant fusion proteins and its related yeast technologies[75].

ANTIBODIES TO GLP-1 AGONISTS

Therapeutic proteins/peptides with structural similarity to endogenous proteins/peptides often have unwanted immunogenicity. Antibodies to the GLP-1 agonists have been described and may inhibit the action of the agonist. The role of antibody formation to the various agonists on the market at present are uncertain. A study by Buse *et al*[76] in 2011 suggested that antibodies to liraglutide did not inhibit efficacy however antibodies to exenitide, if they were high, was associated with a smaller HbA1c reduction. Antialbiglutide antibodies developed in 2.5% of patients in an 8 wk trial.

GLP-1 AND THE CARDIOVASCULAR SYSTEM

Endothelial dysfunction is a common finding in diabetes and an early marker of atherosclerosis. GLP-1 has been shown to improve endothelial dysfunction[77,78]. GLP-1 exerts a cardio-protective effect against ischaemic damage and heart failure. Diabetes is associated with an increased risk of atherosclerosis and myocardial infarction.

Ischaemic preconditioning is a protective mechanism by which the heart may protect itself from prolonged ischaemia. The University Group Diabetes Programme report[39], more than 40 years ago, suggested that tolbutamide might increase myocardial infarction and mortality. Glibenclamide has been shown to affect ischaemic preconditioning but trials have not shown beyond doubt that it is associated with increased myocardial infarction. However drugs that inhibit the K ATP channel opening, such as glibenclamide, are related to loss of ischaemic preconditioning[79-81]. GLP-1 receptors are found in the heart. Increased glucose uptake by the cardiac myocyte is beneficial in protecting the heart from ischaemia changes[82]. Studies in situ and *ex-vivo* suggest a beneficial effect on the heart muscle when under ischaemic stress. Bao *et al*[83] examined the effect of albiglutide in rats after myocardial ischaemia reperfusion injury. They measured cardiac glucose uptake and cardiac metabolic flux. They found enhanced glucose uptake and reduced myocardial infarct size and improved cardiac function. It has yet to be shown if this effect also occurs in humans and if myocardial infarct size and mortality will be reduced by GLP-1 agonists. DPP-4 inhibitors have been less well studied in cardiac ischaemic preconditioning. In a study by Rahmi *et al*[84] rapaglinide, a sulphonylurea like drug, inhibited ischaemic preconditioning as measured by stress testing in patients with type 2 diabetes who already had evidence of coronary atherosclerosis. Vildagliptin, a DPP-4 inhibitor, did not alter preconditioning in 72% of patients whereas 83% of the repaglinide patients had ischaemia earlier in their stress test.

GLP-1 AND THE PANCREAS

Pancreatitis has been described in patients using GLP-1 agonists. A report in 2010 stated that 8 cases during clinical development and 36 post marketing reports are available[85]. A recent report[86] examined a large United States health insurance claims database and could find no increased risk of acute pancreatitis using twice daily exenatide. However there were several limitations to the study and it was a pity that other GLP-1 agonists were not investigated at the same time but the study was funded by Amylin and Eli Lilly. Stimulation of GLP-1 receptors that are found in the exocrine pancreas might lead to overgrowth of the epithelial cells in the small ducts causing pancreatitis through obstruction. A worry has been raised that GLP-1 agonists may induce metaplasia and premalignant changes[87,88].

GLP1 AND THE THYROID

The thyroid contains GLP1 receptors and Gier *et al*[89] also found coincident immunoreactivity for calcitonin and GLP-1 receptors in both medullary thyroid carcinoma and C cell hyperplasia. C cell carcinoma of the thyroid has been seen in animals dosed with GLP-1 agonists and can be explained by the finding of GLP-1 receptors in the thyroid[89]. GLP-1 receptor immuno-reactivity was also found in 18% of papillary thyroid carcinoma. The authors speculate on the consequences of long term stimulation of these GLP-1 receptors. They suggest that prospective studies need to be done to exclude an increase in papillary and medullary carcinoma in the thyroid.

DPP-4 INHIBITORS

These drugs act by inhibiting the enzyme that breaks down GLP-1, thus increasing the level of GLP-1 in the blood stream. They are however not able to raise the GLP-1 levels to levels found after injection of GLP-1 agonists and therefore their hypoglycaemic efficacy is less than that of GLP-1 agonists. Sitagliptin, vildagliptin, saxagliptin and linagliptin have already been approved in the United States and in Europe. An excellent systematic review and meta-analysis has been published in the British Medical Journal in 2012[90]. Compared with metformin, DPP-4 inhibitors were associated with a smaller decline in HbA1c and a lower chance of attaining a HbA1c goal of less than 7%. As a second line treatment DPP-4 inhibitors achieved a smaller decline in HbA1c than the other hypoglycaemic drugs. There was however, no significant difference in attaining an HbA1c of less than 7% when compared to sulphonylureas. They were less effective in lowering body weight when compared to metformin. When added to metformin they had a favourable weight profile compared to metformin and sulphonylureas or pioglitazone but not when compared to GLP-1 agonists. Hypoglycaemia was less common when a DPP-4 inhibitor was added to metformin as compared to a sulphonylurea added to metformin. There is evidence to suggest that the DPP-4 inhibitors are more effective in lowering glucose in Asians than non Asians[91]. A one year follow up of DPP-4 inhibitors *vs* sulfonylureas on top of metformin has been published recently[92]. Patients with prior metformin therapy received a dual combination of metformin with either DPP-4 inhibitor or sulfonylureas. There was no significant difference in either body weight or HbA1c. Hypoglycaemia was significantly less in the patients taking DPP-4 inhibitors. These patients had significantly less transitory cerebral ischaemic attacks whereas other cardiovascular events were of borderline significance.

There are 6 DPP-4 inhibitors (*e.g.*, Sitigliptin, Linagliptin, Vildagliptin, Alogliptin, Saxagliptin, Teneligliptin) on the market minor variation in their chemical composition have not been translated to particular benefit although it should be noted that linagliptin is mostly excreted in pathways other than the kidney and hence dosage does not have to be reduced in moderate renal failure.

Vildagliptin, a DPP-4 inhibitor which increases circulating GLP-1 levels, has been shown to ameliorate the deposition of amyloid beta and tau phosphorylation in a streptozotosin induced animal model of diabetes[93]. A study by Omar *et al*[94] using a high fat diet induced obesity model in mice of advanced age has demonstrated that Vildagliptin confirms other rodent models of diabetes in preserving beta cell mass mainly through inducing beta cell proliferation and reducing beta cell apoptosis[94-96].

Omar *et al*[94] found that Vildagliptin improved glucose secretion in response to oral glucose. Beta cell area was not significantly altered by Vildagliptin treatment in these mice but peri insulitis was prevented by Vildagliptin. Sitagliptin has also been shown to protect against amyloid associated beta cell loss but its effect was not different to that of Metformin[97].

The binding modes of these drugs has recently been investigated[98]. Based on their binding sites the authors divided the drugs into 3 categorise, Vildagliptin and Saxagliptin, Alogliptin and Linagliptin, Sitagliptin and teneligliptin. It is not clear whether these different binding modes have clinical relevance but may help in the development of better inhibitors in the future. Unlike GLP-1 agonists the DPP-4 inhibitors do not pass the blood brain barrier and have no effect on satiety, nor do they effect gastric emptying. Although the different DPP-4 inhibitors have some differences including potency, half lives and metabolism there does not seem to be any meaningful difference in their ability to lower blood sugar and this is probably why there are virtually no head to head studies (one head to head study showed no difference between saxagliptin and sitagliptin when combined with metformin[99]. A good review of the differences has been written by Capuano *et al*[100]. Most of the DPP-4 inhibitors can be administered once daily but Vildagliptin needs to be given twice daily. Saxagliptin is mainly metabolised by CYP3A4/5 isoforms to a major active metabolite 5-saxahydroxygliptin. It is suggested that the dosage of saxagliptin be modified if co administration with CYP3A4/5 inducers such as rifampicin or inhibitors such as ketoconazole.

SITAGLIPTIN

Insulin glargine *vs* sitagliptin another DPP-4 inhibitor was studied by Aschner *et al*[101]. About 250 patients in each group were studied for more than 6 mo. At the start patients were already on metformin which was continued during the study. HbA1c was significantly lower in the glargine group. There were more hypoglycaemic episodes and slight weight gain in the glargine group where as there was slight weight loss in the Sitagliptin group. A recent study compared the effect of sitagliptin or glibenclamide in addition to metformin and pioglitazone on glycaemic control and beta cell function[102]. Body weight reached was lower with sitagliptin. Fasting plasma insulin and homeostasis model assessment of insulin resistance with glibenclamide were significantly increased with glibenclamide and decreased with sitagliptin. Sitagliptin did not change the homeostasis model assessment of beta cell function but the value was significantly increased by glibenclamide. Both glibenclamide and sitagliptin increased C-peptide.

VILDAGLIPTIN

A 24 wk study in elderly patients was recently published[103]. The study investigated the feasibility of setting and achieving individualised targets over 24 wk for elderly patients (over 70 years of age with type 2 diabetes). The patients who were treated with vildagliptin achieved a 0.6% reduction in HbA1c from a baseline of 7.9% as compared with placebo. There were no tolerability issues as compared to placebo, hypoglycaemic events were 2.2% in the vildagliptin arm and 0.7% in the placebo arm. Individualising goal HbA1c is thought to be appropriate particularly in the frail elderly[104]. The benefit of reducing HbA1c by less than 1% in this age group is uncertain. There seems no doubt that in the frail elderly hypoglycaemia is a very serious threat to health[105,106]. Macrovascular disease/events seem to respond better to blood pressure and lipid interventions than to blood sugar lowering at least in the short term[107] but microvascular damage and retinopathy prevention, particularly in patients who already have significant damage, should make the Physician consider carefully the probable benefit of tighter blood sugar control. Under these circumstances one might not choose a DPP-4 inhibitor since they work better in the higher blood sugar range and are less likely to result in the achievement of a HbA1c of 6.5% (48 mmol/L). The efficacy and safety of vildagliptin in patients with type 2 diabetes inadequately controlled on Metformin and sulphonylurea suggests that a mean HbA1c of 8.75% can be improved by about 0.75% as compared to placebo[108]. It is such a pity that the GLP-1 agonists work best at high HbA1c levels and are less effective in reduction of HbA1c as the HbA1c gets near to target. However in this trial 25% more patients reached a target of 7% as compared to controls(38.6% *vis* 13.9%).

SAXAGLIPTIN

The 4-year safety of saxagliptin has recently been published[109]. No new safety issue findings appeared during the 4 years of treatment alone or with metformin and hypoglycaemia did not increase the risk of hypoglycaemia. The cardiovascular safety of diabetic drugs continues to raise concern[109]. Saxagliptin was examined by Scirica *et al*[110]. They randomised 16492 patients with type 2 diabetes who had a history of or who were at risk for cardiovascular events, to receive Saxagliptin or placebo and followed them for a median of 2.1 years. The HbA1c at the beginning of the study was 8.0% and at the end of the study the HbA1c in the Saxagliptin arm had decreased to 7.5% and the placebo arm to 7.8%. A surprising finding was that more patients in the Saxagliptin group were hospitalised for heart failure but otherwise the cardiovascular end point results were similar between the two groups. Hospitalisation for hypoglycaemia occurred infrequently and was similar in the two groups but significantly more patients in the saxagliptin group reported at least one hypoglycaemic event. Thus this 2-year study gives little support for the use of saxagliptin in these patients.

LINAGLIPTIN

Linagliptin is a once a day oral DPP-4 inhibitor. It is an

orally active small molecule which was licensed in United States in 2011. It is mostly excreted in the faeces and there are no clinically relevant alterations in linagliptin pharmokinetics resulting from renal or liver impairment[111]. A recent study has confirmed that renal impairment has no clinically relevant effect on the long term exposure of linagliptin in patients with type 2 diabetes[112].

A 2-year efficacy and safety study of linagliptin compared to glimepiride in patients inadequately controlled on metformin was reported recently[113]. More than 1400 patients were divided into two groups. HbA1c at the end of the study was similar in the two groups but there was less hypoglycaemia and there were significantly less cardiovascular events (1 *vs* 2). Hypoglycaemia is not usually a problem in the treatment of type 2 diabetes but recently has been suggested to be a therapeutic concern. The efficacy and safety of Linagliptin in subjects with type 2 diabetes was analysed by Del Prato *et al*[114]. Pooled analysis of data from 2258 subjects in 324 wk phase 3 studies. Oral linagliptin or placebo as monotherapy added on to metformin or added on to metformin plus a sulphonylurea were the treatments investigated. Although linagliptin was effective the patients had a mean HbA1c of 9.0% and the level of HbA1c only dropped to 8.3% still unacceptably high for many patients. DPP-4 inhibitors unfortunately work less well the lower the starting HbA1c[102]. A study of linagliptin in patients aged over 70 years found that HbA1c was lowered by 0.64% from 7.8% to 7.2% with a safety profile similar to placebo. Whether long term studies in this age group will show benefit in measurable outcome is speculative at this time.

ALOGLIPTIN

Alogliptin seems to have much the same characteristics as the other DPP-4 inhibitors on the market, A useful review has recently been published[115]. Another large study specifically looking at cardiovascular disease in type 2 diabetic patients has been reported[116]. More than 5000 patients who had type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalisation within the previous 15 to 90 d received allogliptin or placebo in addition to existing antidiabetic and cardiovascular drug treatment. HbA1c at the start of the trial was 8.0% and at the end of the study had come down to 7.7% as compared to 7.97% in the placebo group. Hypoglycaemia was similar in the two groups. Again this large study makes one question the value of the addition of the DPP-4 inhibitor which was associated with such a modest drop in HbA1c.

TENELIGLIPTIN

Teneligliptin is another DPP-4 inhibitor which has been recently reviewed[117].

DPP-4 INHIBITORS AND THE HEART

GLP-1 receptors, which are found in the heart increase glucose uptake by the cardiac myocyte is beneficial in protecting the heart from ischaemia changes[118]. Matsubara *et al*[119] examined 44 patients with coronary artery disease and uncontrolled diabetes (HbA1c > 7.4%). Sitagliptin or aggressive conventional treatment was compared after 6 mo. Endothelial function was significantly improved in the sitagliptin group with no difference in fasting blood sugar at the end of the trial but a reduction in HbA1c of 0.6% in each group. C-reactive protein (CRP) reduced significantly in the sitagliptin group with a significant correlation between the CRP and the vascular reactivity but not with HbA1c.

DPP-4 INHIBITORS AND THE PANCREAS

Butler *et al*[120] examined the pancreata of 7 individuals treated with sitagliptin and 1 with exenatide compared with 12 individuals with type 2 diabetes treated with other agents, and 14 non-diabetics. There was an increase in the number of pre-malignant lesions and marked alpha cell hyperplasia with glucagon expressing micro adenomas and a glucagon expressing neuroendocrine tumour in one of the eight. Because the number of diabetics who were not on treatment with DPP-4 based therapy were so few the evidence is insufficient for alarm but the evidence for caution and vigilance in the next number of years is clear and persuasive.

Sero negative polyarthropathy has been recorded with the use of DPP-4 inhibitors. Three patients were described by Crickx *et al*[121] and one case by Ambrosio *et al*[122]. The acute arthritis is not perhaps surprising since DPP-4, also named CD 26 is expressed on many cells involved in the immune process.

CONCLUSION

New treatments for diabetes are coming on line but prevention and treatment of obesity through increased exercise and reduced calorie intake still seems the best option in most patients with type 2 diabetes. Those with insulin deficiency have new options which are exciting as they demonstrate new approaches to treatment but their glucose lowering effects are modest and mostly most effective when blood sugars are high thus of less use when blood sugars are near to, but not at, target in spite of a combination treatment.

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