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Hyp-O-besity: Unmet Challenge in Management of Type 2 Diabetes Mellitus and Cardiovascular Risk

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Abstract

Glycaemic control is often disturbed by iatrogenic hypoglycaemia as a result of intensive and can be a major barrier to optimal glycaemic management. This risk of hypoglycaemia acts like a deterrent to the patient from achieving euglycaemia. The fear of hypoglycaemia leads to "defensive snacking" which further disrupts achievement of euglycaemia and leads to weight gain. Obesity by itself carries a major risk for adverse cardiovascular outcomes and coupled with hypoglycaemia significantly increases the cardiovascular risk in patients with diabetes. "Hyp-o-besity" is a new term that effectively conveys the present challenges in achieving euglycaemia due to hypoglycaemia and obesity and would help facilitate therapeutic strategies to optimise diabetes management. Newer drugs targeting the incretin pathway such as glucagon-like peptide-1 (GLP-1) mimetic and dipeptidyl peptidase-4 (DPP-4) inhibitors would be beneficial in minimising the risk of hypoglycaemia and obesity.

Keywords: Glycaemic control; Cardiovascular disorders; Obesity; Hypoglycaemia; Pharmacological management of diabetes

Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Study Group; ADA: American Diabetes Association; ADOPT A: Diabetes Outcome Progression Trial; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial; CAD: Coronary artery disease; CAROLINA: Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes; CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; DCCT: The Diabetes Control and Complications Trial; DPP-4: Dipeptidyl peptidase-4; EASD: European Association for the Study of Diabetes; EDIC: Epidemiology of Diabetes Interventions and Complications; EMA: European Medical Agency; GLP-1: Glucagon-like Peptide-1; HR: Hazard Ratio; IDF: International Diabetes Federation; IDMPS: The International Diabetes Management Practices Study; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NIH: National Institutes of Health; OADs: Oral Antidiabetic Drugs; OHDs: Oral Hypoglycaemic Drugs; SGLT2: Sodium Glucose Transporter 2; SU: Sulphonylurea; T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; TZDs: Thiazolidinediones; UKPDS: United Kingdom Prospective Diabetes Study; US FDA: Food and Drug Administration; VADT: Veterans Affairs Diabetes Trial

Introduction

The prevalence of diabetes in 2014 was 382 million which was estimated to scale up to an alarming 592 million by 2035 by the International Diabetes Federation (IDF). Nearly 80% of people with diabetes are in the low and middle income countries [1]. Moreover greater than 60% of world diabetes population will be in Asia. India, Nepal and China have shown an increasing prevalence of diabetes even among the rural population. The fact that India and China have large rural populations may contribute to the overall increase in national prevalence [2].

The escalating rate of obesity is a major causative factor for increasing prevalence of Type 2 diabetes (T2DM) [3,4]. The prevalence of overweight is increasing in Asian countries mainly in China and in India, together with an increasing trend of childhood obesity. This has been associated with a concurrent increase in diabetes prevalence [5,6].

Majority of the data regarding obesity and its adverse health effects such as glucose intolerance, atherosclerosis or increased risk for cardiovascular disease are derived from Europe, Canada or United States. However health risks associated with obesity occur in people with lower body mass index (BMI) in the Asia-Pacific region. The South Asian population has several unique characteristics, such as: young age of onset of diabetes, a relatively lower BMI at time of diabetes diagnosis with accompanying insulin resistance, and reduced insulin secretory capacity. According to the epidemiological study by our group, the normal cut-off value for BMI is 23 kg/m^2 for both sexes. Cut-off values for waist circumference were 85 and 80 cm for men and women, respectively; the corresponding waist to hip ratios was 0.88 and 0.81, respectively [7]. The World Health Organization (WHO) recommends lowered cut-off points for overweight and obesity for Asians in the Asia Pacific region (overweight: BMI ≥ 23 kg/m^2 in comparison with ≥ 25 kg/m^2 for western populations). This body type is termed as thin-fat phenotype (thin muscle but fat body) and is associated with an increased risk of developing diabetes [8].

American Diabetes Association (ADA) guidelines recommend weight loss for all overweight or obese individuals who have /are at risk for diabetes. Weight reduction is especially important in Asians who have lower cut-offs for overweight and obesity and hence are

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highly predisposed to development of diabetes and worsening of diabetes [9]. A retrospective cohort study conducted by Shantha et al. [10] in 2012 demonstrated that intentional weight loss of 10% in obese individuals with T2DM could potentially decrease percentage glycated haemoglobin (HbA1c) by 0.81%.

The objective of this review is to explore the various aspects of this relationship between obesity and T2DM and its association with hypoglycaemia and weight gain which is two common adverse effects associated with a few anti-diabetic medications. It also discusses the various proposed mechanisms underlying hypoglycaemia and obesity. The ethnic differences, role of patient education and the importance of newer treatment approaches in the management of diabetes especially in managing the weight gain associated with hypoglycaemia have also been highlighted.

Current Practice Patterns and Shortfalls

Sulfonylureas (SUs), biguanides, and thiazolidinediones (TZDs) are the routinely used oral antidiabetic drugs (OADs) in the treatment of T2DM. Current treatment guidelines recommend metformin as the first pharmacological agent to be added to therapeutic lifestyle changes for the majority of patients unless contraindicated [11,12].

Current Guidelines

According to the latest ADA/ European Association for the Study of Diabetes (EASD) consensus statement, metformin and/or lifestyle intervention is the first line of pharmacological monotherapy to treat T2DM patients. If the target HbA1c (<7.0%) is not achieved within 3 months, then basal insulin, SUs, glitazone, DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitors can be added as the second line of therapy. A three-drug approach may be needed if the HbA1c target is not achieved within 3 months of two-drug combination therapy. In individuals on combination therapy with basal insulin and not achieving glycaemic target goals, complex insulin strategy (multiple daily doses) with one or two non-insulin agents is recommended [12].

Metformin monotherapy is capable of lowering HbA1c by 1.5% and is generally well tolerated with lower risk of hypoglycaemia. Metformin also provides either weight stability or modest weight loss in contrast to several other OADs [12].

Metformin monotherapy as studied in the United Kingdom Prospective Diabetes Study (UKPDS) trial resulted in sustained glucose lowering for more than 2 years on an average; however, a secondary failure rate of 5% to 10% per year was noted [13]. Progression of the disease with progressive beta-cell dysfunction makes it difficult for patients to achieve glycaemic targets with metformin monotherapy. The UKPDS, a Diabetes Outcome Progression Trial and other trials found high rates of secondary failure with all current oral hypoglycaemic drugs, including successful initial metformin therapy. The addition of SU to metformin has been the conventional and gold standard combination therapy for decades [14].

SUs are as effective as metformin in lowering HbA1c, but its use is associated with hypoglycaemia and weight gain up to 2 kg [12]. It has also been found that though they are effective in lowering the blood glucose rapidly in the initial phase of therapy, this effect is not sustained over time. SU therapy was implicated as a potential cause of increased cardiovascular disease mortality in the University Group Diabetes Program study [15].

TZDs, also known as insulin sensitizers, appear to have a more durable effect on glycaemic control, particularly in comparison with SUs. However, TZDs lead to weight gain, fluid retention, peripheral oedema, and a two-fold increased risk for congestive cardiac failure [15-18]. The US Food and Drug Administration (FDA) has recommended black box warnings on rosiglitazone indicating an increased risk of congestive heart failure [19]. Similarly, the US FDA and European Medical Agency (EMA) recommend that pioglitazone should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer or in patients with un-investigated macroscopic haematuria [20].

All the above pharmacological drugs focus on reducing hyperglycaemia and improving insulin sensitivity. These drugs are theoretically attractive, as they appear to target the primary defects associated with T2DM. However, despite the wide choice of treatment options available, glycaemic control declines over time and eventually combination of OADs is required [15].

It is important to consider that while the median use of OAD's with or without insulin was around 70% across the globe, India was associated with a higher usage of OADs at >90%. As per studies conducted in the late nineties, SU were the most commonly prescribed drugs in most countries including India [21]. The trends have changed over this period with metformin use having increased from 30% to 60% between 1997 and 2003 alone [22]. However challenges remain in the optimal use of OADs.

Unmet Clinical Challenges

Diabetes is the major cause of premature illness and death in most countries and is a leading cause of cardiovascular diseases, blindness, end-stage renal failure, amputations and hospitalizations [23]. Chronic complications of diabetes mellitus are primarily responsible for majority of morbidity and mortality [24]. National Diabetes Information Clearing house, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institutes of Health (NIH) data have found that 65% of people with diabetes die of some form of heart disease or stroke. Diabetes mellitus significantly increases the risk of mortality in the presence of cardiovascular disease (Hazard Ratio, 2.2 for women and 1.7 for men) and all-cause and cardiovascular mortality rates among individuals with T2DM remains approximately 2-fold higher compared with individuals without T2DM [25]. Mortality is bound to increase in India, China, United States of America and the Russian Federation with a greater risk for women compared with men [23]. Asia-Pacific Cohort Studies Collaboration (APCSC) has found that population attributable fractions for diabetes ranged from 2% to 12% for coronary heart disease [26]. The International Diabetes Management Practices Study (IDMPS) reported that the expected annual rates of diabetes related hospitalizations were 2.6, 2.9 and 2.4 times greater for patients with microvascular diseases and 3.2, 3.1 and 4.6 times greater for patients with inadequate glycaemic control in all three regions including Asia, Latin America and Middle- East- Africa respectively [27].

Cardiovascular Diseases (CVD) mortality correlated with increased two hour plasma glucose and was found to be twice in patients with diabetes in several well conducted prospective studies [28].

This data denotes that there still exists an apparent unmet clinical challenge of higher prevalence of micro and macrovascular complications, increased cardiovascular risk, hospitalization, increased morbidity and mortality and poor glycaemic control. Early intensive glycaemic control is supported by current international guideline recommendations and backed by outcome data from long term clinical trials [12].

Role of early intensive glycaemic control

The UKPDS and the Diabetes Control and Complications Trial (DCCT) confirmed that microvascular complications like nephropathy, retinopathy, and neuropathy have a strong correlation with HbA1c levels. Vascular complications may progress in patients with HbA1c <7.0% and may appear even in undiagnosed patients secondary to transient increases in blood glucose concentrations. Macrovascular complications often develop early and may not correlate linearly with HbA1c. Therefore managing hyperglycaemia in the later stages of T2DM may not be associated with improved cardiovascular outcomes [29].

All current international guidelines recommend the need to achieve and maintain glycaemic control to near normal range to prevent microvascular complications in type 1 (T1DM) and T2DM. This rationale is based on the emerging pattern evident from several clinical trials that have shown that long term management of diabetes mellitus with intensive glycaemic control helps achieve glycaemic control, prevent micro vascular and macro vascular complications further reducing the mortality and morbidity rates [12].

The UKPDS over a 6 year follow-up found an overall reduction rate of 25% for microvascular complications due to intensive glycaemic control (intensive therapy of insulin, sulfonylurea [chlorpropamide or glyburide] or metformin). With every percentage point decrease in HbA1c, there was a 25% reduction in diabetes related death, 7% reduction in all-cause mortality and 18% reduction in combined fatal and nonfatal myocardial infarction [13,14]. The DCCT over an average of 6 years (range 3-9 years) found a 60% reduction in diabetic retinopathy, nephropathy, and neuropathy with intensive regimen [30].

The phenomenon of metabolic memory emerged in the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) trial of DCCT in T1DM patients. EDIC data showed that there was a lower incidence of microvascular diabetic complications in patients who were in the intensive regimen group in the prior DCCT trial compared to standard group in spite of nearly equal HbA1c levels at baseline (Figure 1a) [31-33]. Post-trial monitoring of 3277 UKPDS patients over a period of 10 years found a relative risk reduction of microvascular disease in the SU–insulin group as well as the metformin group (Figure 1b) [34,35].

Early metabolic control has long-term beneficial effects in management of diabetes mellitus hence there is a need for early aggressive intensive management to normalize metabolic actions [36].

Hypoglycaemia

The estimated average incidence of severe hypoglycaemia ranges from 1.0 to 1.7 episodes per patient per year in patients with T1DM; the DCCT found an incidence of 0.19 to 0.62 episodes per patient per year. It is difficult to estimate incidence of hypoglycaemia in T2DM due to varying definitions and data being used from retrospective studies. Veterans Affairs Cooperative Study (VACS) in T2DM found an overall incidence of 0.02 episodes per patient per year for severe hypoglycaemia [37].

Patients with T2DM become vulnerable to hypoglycaemia over a period of time as the counter regulatory communication between glucagon producing alpha cells and insulin producing beta cells become defective over a period of time. The working groups of the ADA and the Endocrine Society have jointly recommended that a plasma glucose concentration of ≤ 70 mg/dl needs to be considered as the cut-off point for defining hypoglycaemia. The value has been set higher than the thresholds at which hypoglycaemic symptoms usually occur so as to enable patients take appropriate actions before developing hormonal counter regulation [38].

The prevalence of hypoglycaemia in patients with T2DM treated with insulin for >5 years is 25%, a threefold increased risk when compared with individuals exposed to insulin for <2 years. The need of reinforcing the importance of prevention, detection and reversal of hypoglycaemic events becomes essential in all patients with T1DM and in patients with T2DM exposed to insulin for greater than 5 years [38].

It is apparent that the emerging scenario of higher prevalence of obesity, poor insulin sensitivity, increased metabolic risk in Asians at lower BMIs are fuelled by the current practice patterns leading to less than optimal guideline recommended outcomes in diabetes mellitus

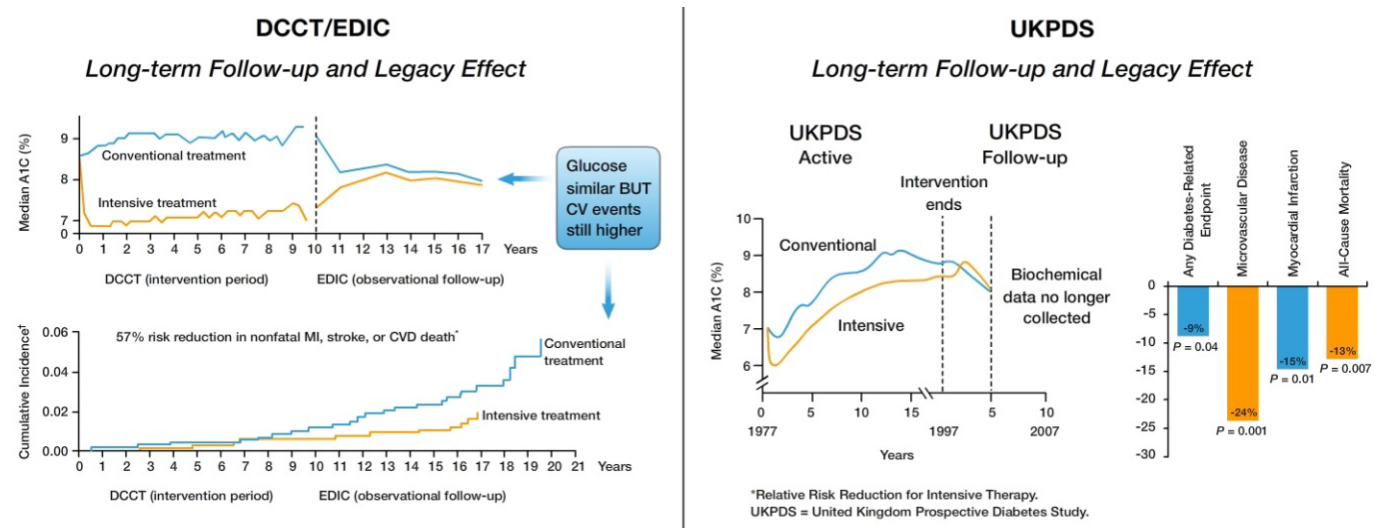

Figure 1: a: DCCT/EDIC Long term follow up and metabolic memory in Type 1 diabetes (T1DM) patients; **b:** UKPDS long term follow up and legacy effect.

[4]. Hypoglycaemia complicates management of diabetes when conventional regimens- insulin and SU are used.

Emerging unmet issues of worsening hypoglycaemia and weight gain with treatment intensification

Obese patients in the UKPDS trial had a greater mean increase in body weight (10.4 kg vs. 3.7 kg). The highest average annual incidence of major hypoglycaemic events was 2.3% of patients per year in those receiving insulin therapies [36,37]. Intensively treated patients in the DCCT trial showed major weight gain, with most significant weight gain occurring during the first year of therapy. They were likely to be more overweight in both the sexes, with a major weight gain of ≥ 5 kg [39,40].

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial (ADVANCE), Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD), Veterans Affairs Diabetes Trial (VADT; minimum of 5 years of follow–up) and ADOPT trial have shown that intensive glycaemic control can lead to hypoglycaemia and weight gain (Table 1).

Meta-analysis by Levetan et al. [46] showed that most OADs including glipizide XL, glyburide, glimepiride, repaglinide lead to hypoglycaemia. Weight gain is associated with glipizide XL, glyburide, glimepiride, repaglinide, rosiglitazone and pioglitazone. Therefore it is apparent that current strategy of intensive glycaemic control to prevent micro and macro vascular complications leads to emerging unmet issues of hypoglycaemia and weight gain.

Hypoglycaemia and vascular complications

Hypoglycaemia may increase the risk of ischemia and sudden death in individuals with T2DM [47]. Hypoglycaemia in patients with T2DM demonstrated a 65% increase in the odds of myocardial infarction. The risk of myocardial infarction remained elevated by approximately 20% for up to six months following a hypoglycaemic event [48].

VADT trial showed that severe hypoglycaemic event was an important predictor for CV death (HR 3.72; 95% CI 1.34–10.4; P<0.01) and all-cause mortality (Hazard Ratio 6.37; 95% CI [2.57–15.8]; P=0.0001). However in ADVANCE trial there was no increase in all-cause or cardiovascular mortality with severe hypoglycaemia. Although the trials provided different results, severe hypoglycaemia was strongly associated with increased cardiovascular risks [49]. Severe hypoglycaemia is associated with significant morbidity including major vascular events such as myocardial infarction or stroke. In patients who had myocardial infarction, spontaneous hypoglycaemia was associated with a 2-fold increase in mortality. The possibility of decrease in myocardial blood flow reserve might lead to cardiovascular mortality in hypoglycaemic patients [50,51]. Khan et al. [52] assessed effect of acute hypoglycaemia on retinal function which showed decrease in retinal response in T1DM with reduced amplitude of response in central macular retina and central scotoma.

Position statement of the ADA and the EASD recommended that in view of the high risk of developing atherosclerosis with diabetes, optimal management strategies are necessary in patients with or at high risk for Coronary Artery Disease (CAD) especially in patients with hypoglycaemia exacerbating myocardial ischemia and leading to dysrhythmias. It is important to choose the right OAD for optimal management of these patients. SU may aggravate myocardial ischemia; metformin may improve cardiovascular outcomes and pioglitazone may reduce major adverse cardiovascular events in patients with established macro vascular disease [12].

Hypoglycaemia impacting long term outcomes

Glycaemic control is often disturbed by iatrogenic hypoglycaemia and can be a major barrier to optimal management of glycaemic control. The physiological and behavioural defences against hypoglycaemia eventually get compromised in most patients with T1DM and advanced T2DM eluding euglycemia and causing recurrent morbidity. Hypoglycaemia is especially dangerous in the elderly and is seen more frequently when the glycaemic targets are lowered in these patients. In these patients, it may lead to dysrhythmias, accidents and falls, dizziness (leading to falls), confusion or infection (hypoglycaemia in the night may lead to aspiration during sleep and consequently pneumonia) [53].

Drug selection would probably play an important role in preventing hypoglycaemia and reaching target goals [12]. Pharmacological management with insulin or OAD's may lead to intake of excess calories to manage or prevent hypoglycaemia; this along with habitual overeating may lead to a vicious cycle of increased caloric intake leading to weight gain which in turn increases insulin resistance and occurrence of diabetes. Retrospective epidemiological analysis of the ACCORD study found that recognized and unrecognized hypoglycaemia was more common in the intensive regimen compared to standard therapy (1.06 episodes vs. 0.29 episodes). A small but statistically significant inverse relationship between frequency of hypoglycaemic episodes and mortality was seen with the intensive group compared to standard group {HR [0.93 (95% CI 0.9–0.97; P < 0.001)] vs. HR [0.98 (0.91–1.06; P = 0.615)]} [54,55].

Awareness of hypoglycaemia

T2DM is associated with a substantial incidence rate of hypoglycaemia [56,57]. Hypoglycaemia is a major deterrent in management of diabetes leading to increased morbidity, increased risk of microvascular and macrovascular complications and reduced

Study	Years of follow-up	Drugs	BMI &Weight gain in kg	Hypoglycaemia
UKPDS [13,14]	6	Insulin vs. sulfonylurea	9.9 vs. 5.3 kg in the primary diet failure group Obese patients had a greater mean increase in body weight (10.4 vs. 3.7 kg)	52% (insulin; 2.3% per year) 16% (chlorpropamide) 21% (glyburide)
DCCT [39,40]	6.5	Insulin (multiple daily insulin injections or continuous subcutaneous infusion)	BMI: 1.5-1.8 kg/m^2 Average weight gain of 4.75 kg in the intensive group	3-fold higher in the intensive group
ADVANCE [41,42]	5	Gliclazide and other drugs	0.7 kg	Severe hypoglycaemia more common in the intensive group
ACCORD [43,44]	3.5	Sulfonylurea and other drugs	>10 kg	More frequent in the intensive therapy group
ADOPT [45]	4	Rosiglitazone vs. Glyburide	4.8 vs. 1.6 kg	Fewer episodes vs. more episodes

Table 1: Weight Gain and Hypoglycaemia in Several Clinical Landmark Trials.

quality of life. Patient's fear of hypoglycaemia can lead to chronic over-eating termed as 'defensive snacking' which leads to weight gain [58].

Patients with unawareness of hypoglycaemia are generally at higher risk of hypoglycaemia; however patients with reduced awareness are at a higher risk of moderate and severe hypoglycaemia especially patients with T1DM [59]. Hypoglycaemia unawareness is also more common in advanced T2DM [60].

Rebound hyperglycaemia: Correlation with hypoglycaemia

Patients with diabetes with inadequate food intake or taking more insulin before bedtime can experience rebound hyperglycaemia. This usually follows a high blood glucose levels in the morning preceded by an episode of hypoglycaemia between 2.00 am to 3.00 am in the morning. In response to low blood glucose in the middle of the night, the body counters by releasing the hormones namely cortisol, catecholamine and growth hormone to raise the sugar levels.

Repeated hypoglycaemia is common in patients on injected insulin or insulin secretagogues. Patients may consume large quantities of carbohydrates to counter this and are then inadvertently at a high risk of rebound hyperglycaemia [61].

Hypoglycemia and gastric bypass surgery

Researchers have observed a relationship between gastric bypass surgery and symptomatic hypoglycemia (Dumping Syndrome) and in rare cases the development of nesidioblastosis. In the dumping syndrome there is quick absorption of nutrients from the jejunum triggering an excessive release of insulin resulting in hypoglycemia. Improvement in insulin sensitivity secondary to weight loss, absence of reversal in the number of beta cells producing insulin and stimulation of insulin secretion due to excessive secretion of GLP-1 have been postulated mechanisms for the development of hypoglycemia in this scenario [62].

Role of patient education and lifestyle intervention

Review of medications with the patients and family members should be done on a regular basis. Recognition of symptoms of hypoglycaemia and management should be discussed at each visit. The physicians should guide the patients about the quantity of carbohydrate to be consumed in order to overcome a hypoglycaemic event based on the blood glucose level. The physician should make aware about the various dietary options which provide instant carbohydrate. The below mentioned formula can help the patients in overcoming a hypoglycaemic event. (100 − blood glucose) 0.2 = g of carbohydrate needed for appropriate blood glucose correction) [38].

Self-Monitoring of Blood Glucose (SMBG): The physicians should also make aware of the dissociated meal and injection patterns which can lead to glycaemic fluctuations and hypoglycaemia. The administration of insulin either 15 minutes before or after meals should be adjusted in such a way that the rise in insulin levels coincides with the peak carbohydrate absorption from the gut. The risk of exercise-induced hypoglycaemia may be obviated by carrying out SMBG before and within 30 minutes of exercise sessions. It should be ensured that the pre-exercise glucose target should be kept at 120-180 mg/dl. Consumption of 15 g of carbohydrate before exercise can help in overcoming low blood sugar levels after exercise. Similarly the dose of prandial insulin should be reduced by 50% if exercise is scheduled within 4 hours of administration of prandial insulin. Renal clearance of medications may be delayed in patients with chronic kidney disease and their doses should be adjusted when their creatinine clearance is <50 ml/min/1.73m^2. The exceptions include liraglutide and linagliptin wherein dose adjustments may not be required. The treating doctor should also make the patients aware of the availability of CGM devices which provides real-time notification of impending events [38].

Impact of weight gain

Weight gain can lead to significant impact on lifestyle and cardiovascular diseases with the propensity for diabesity [63-66]. Co-existent diabetes and obesity termed as diabesity is an emerging epidemic which can present a challenging scenario for management and further increases the risk of morbidity and mortality. Obesity increases the risk of hypertension and dyslipidaemia contributing to the overall cardiovascular risk profile. Obesity along with hyperglycaemia and other risk factors such as smoking, hypertension, dyslipidaemia can increase all-cause mortality and cardiovascular mortality in patients with diabetes [63,67]. Framingham study has shown that 2.25 kg increase in weight over 16 years is associated with 20% rise in the summed severity of six cardiovascular disease risk factors in men and 37% increased risk in women and 78.8% women and 86.9% men with obesity and diabetes have a 30-year risk of developing cardiovascular disease. Swedish National Diabetes Register study showed that among overweight/obese T2DM patients who gained weight per 1 unit increase in BMI there was a 13% increased risk of fatal and nonfatal Coronary Heart Disease (CHD) [68]. Patients with higher BMI have been found to have more severe retinopathy (P<0.0001) and neuropathy (P=0.007) in T1DM [69]. Weight gain attributable to pharmacotherapy may further lead to increased frustration in these patients leading to premature discontinuation of drugs or poor adherence. Delay in initiation of insulin therapy and non-compliance may also result due to weight gain. Obesity leads to a vicious cycle of insulin resistance, progression of diabetes with current management of intensive glycaemic control. Obesity is a major deterrent in the management of diabetes mellitus [68].

Insulin pumps: Hypoglycaemia and weight gain

Patients achieving glycaemic control by infusion pumps had lower episodes of hypoglycemia when compared to their pre pump years. The decrease in severe hypoglycemia is attributed to proper planning, frequent blood glucose checks, decreasing basal insulin infusion rates during and after heavy exercise, checking basal rates and bolus accuracies. Patients with diabetes who achieve better glycemic control with insulin therapy may gain weight as the glucose will be expended for energy purposes rather than being eliminated in urine. However, few patients may tend to eat more as it is easy to push buttons to administer an extra dose of insulin when compared with an injection [70].

Newer Treatment Options

The present standard of care and pharmacological therapy for diabetes is unable to meet the unmet real world clinical challenge of hypo-obesity. There is a need for novel and newer drug therapies to effectively prevent complications of current management therapy-hypoglycaemia and obesity. The newer drugs include glucagon-like peptide-1 (GLP-1) mimetic, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose transporter 2 (SGLT2 inhibitor) and long acting and intermediate acting insulin analogues [71,72].

GLP-1 analogues slow gastric emptying and increase satiety, which is responsible for weight loss and have been associated with a significant reduction in mean body weight from baseline (−2.1 ± 0.2 kg), with progressive reductions over 2 years (−4.7 ± 0.3 kg) [73].

A meta-analysis of 13 trials including DPP-4 inhibitors

vildagliptin, saxagliptin and sitagliptin by Dicker et al. [73] has demonstrated that these drugs are weight neutral and were associated with minimal incidence of hypoglycaemia when used as monotherapy or in combination therapy. Other major studies are being conducted to further analyse their effects on cardiovascular outcomes. SAVOR-TIMI 53 was a phase 4, randomized, double-blind, placebo-controlled trial conducted in 25 countries that was designed to evaluate the safety and efficacy of saxagliptin during long-term treatment of approximately 16,500 patients with T2DM. This study concluded that saxagliptin had no effect on the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke in patients at high risk for CV events [74].

Linagliptin, the newest DPP-4 inhibitor (approved by the FDA in May 2011) will be evaluated in the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with T2DM (CAROLINA study), a multicentre, international, randomised, parallel group, double blind study [75].

Amylin mimetic drugs reduce the production of glucose by the liver by inhibiting the action of glucagon and diminishing postprandial glucose fluctuations. They have been shown to be more useful in insulin dependent diabetes when compared with T2DM. The role of dual and PPAR–alpha and gamma agonists in the management of diabetes is presently uncertain following safety concerns like edema and weight gain. However their favourable effect on lipids and glycaemic control encourages further research [76].

Discussion

The Asia Pacific guidelines have lower cut off points for BMI in the overweight and obese category which places emphasis on increased risk of developing diabetes especially in Asians compared with European counterparts [4]. The majority of patients are managed with OADs with or without combination with insulin therapy [21,22].

Ethnic differences in the response to various OADs have been also explored. Findings from the studies have shown that Asian patients have a higher risk of developing T2DM when compared with their Western counterparts. Asian patients are also more vulnerable to abdominal obesity and low muscle mass with increased insulin resistance. Evidences suggests that incretin based drugs tend to exert beneficial effects in Asian patients by improving the defective early phase insulin secretion. Studies have demonstrated that DPP-4 inhibitors exert greater HbA1c lowering in Asians when compared with non-Asians [77].

In spite of the current scenario of diabetes management, recommended drugs and ADA guideline recommendations for weight reduction, majority of patients do not achieve glycaemic control [5,22]. It has also been found that majority of patients are not screened for micro-and macrovascular complications, and have a higher rate of work-related absenteeism and a higher rate of hospitalisation due to vascular complications [21,27]. Patients with diabetes are at an increased risk of cardiovascular mortality and morbidity [1].

The basis of the current pharmacological guideline recommendations have been incorporated over the years based on long term landmark clinical trials (median follow up of 6-10 years) which have proven that tight glycaemic control is necessary to prevent long term microvascular and macrovascular complications and prevent morbidity and mortality due to diabetes mellitus and its complications [12]. However the goal of achieving euglycaemia with intensive glycaemic control is deterred by the occurrence of hypoglycaemia and weight gain. Several clinical trials- UKPDS, ACCORD, ADVANCE, DCCT, VADT, ADOPT have all shown that major weight gain occurs during the first year of intensive therapy and is seen to progress over the years of therapy. These trials have also shown that severe hypoglycaemia usually occurs with intensive glycaemic control [13,14,39-45].

Overweight/ obese individuals have an increased risk of developing T2DM [4]. Obesity by itself predisposes to increased risk of cardiovascular complications [68]. Diabetes also contributes to increased risk by means of microvascular and macrovascular involvement secondary to the lack of euglycaemia [21,27]. Glucose lowering therapy using conventional agents such as SU and insulin are intended to maintain euglycaemia [12]. But as we intensify treatment to achieve euglycaemia, the risk of hypoglycaemia increases [13,14,39-45]. This risk of hypoglycaemia acts like a deterrent to the patient from achieving euglycaemia. The fear of hypoglycaemia leads to "defensive

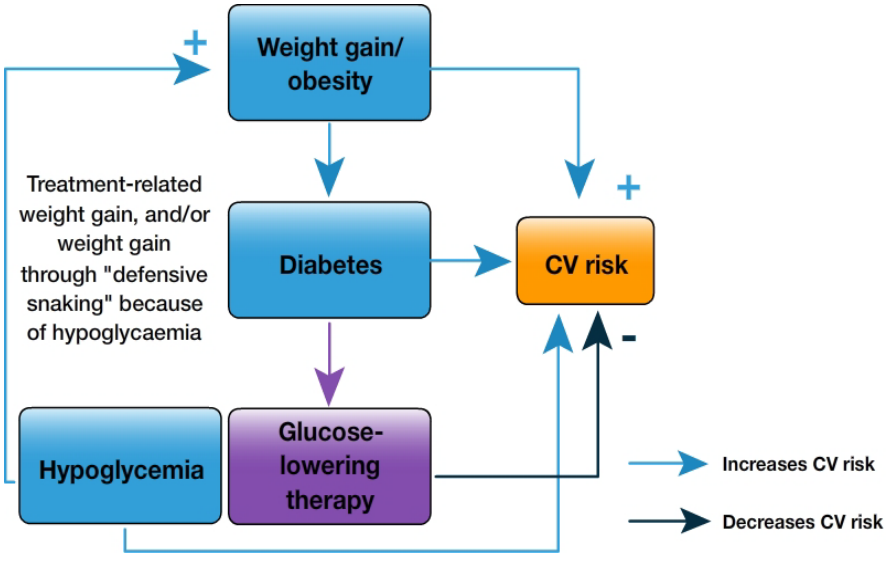

Figure 2: Schematic representation of vicious cycle induced by hypoglycaemia in Type 2 diabetes (T2DM).

snacking" which further disrupts achievement of euglycaemia and leads to weight gain [58]. This vicious cycle of intended euglycaemia leading to hypoglycaemia and weight gain culminating in cardiovascular events due to the existing treatment patterns has been highlighted in Figure 2.

The avoidable but common side effect namely hypoglycaemia puts the patient at increased risk of cardiovascular events in the form of arrhythmias and myocardial ischemia involving the sympathoadrenal response and changes in platelet function [78].

Apart from defensive snacking and dose dependent effects of anti-diabetic medications used for intensive glycemic control, there are other mechanisms which can lead to weight gain in patients with diabetes [79]. These include decreased glycosuria [80], decreased metabolic rate, fluid retention and expansion in adipose tissue [81,82].

There arises a need for coinage of a new term "Hyp-o-besity" effectively implying the present challenges due to hypoglycaemia and obesity in achieving euglycaemic control with conventional drug regimens/insulin therapy in the already obese patients with T2DM. The coinage of this new challenging and complex entity would help increase awareness and focus attention to facilitate the standards of care contributing towards effective management of the current real world challenges faced in the management of diabetes.

Conclusion

There is a need for novel and newer drug therapies to effectively prevent a major complication of current management therapy—'hyp-o-obesity'. The newer drugs targeting the incretin pathway would be beneficial in minimising the risk of hypoglycaemia and obesity, which would lead to optimal management of diabetes mellitus and address the unmet clinical challenge of hypo-obesity currently faced. The possible benefits with reduction in cardiovascular risk and vascular events can be an added advantage.

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References

1. International Diabetes Federation (2013) IDF Diabetes Atlas. (6thedn). The global burden. 29.
2. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A (2012) Trends in prevalence of diabetes in Asian countries. World J Diabetes 3: 110-117.
3. Ramachandran A, Chamukuttan S, Shetty SA, Arun N, Susairaj P (2012) Obesity in Asia--is it different from rest of the world. Diabetes Metab Res Rev 28 Suppl 2: 47-51.
4. Regional Office for the Western Pacific of the World Health Organization, International Association for the Study of Obesity and the International Obesity Task Force (2000) The Asia-Pacific perspective: Redefining obesity and its treatment.
5. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, et al. (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301: 2129-2140.
6. Boffetta P, McLerran D, Chen Y, Inoue M, Sinha R, et al. (2011) Body mass index and diabetes in Asia: a cross-sectional pooled analysis of 900,000 individuals in the Asia cohort consortium. PLoS One 6: e19930.
7. Snehalatha C, Viswanathan V, Ramachandran A (2003) Cutoff values for normal anthropometric variables in asian Indian adults. Diabetes Care 26: 1380-1384.
8. Yajnik CS, Fall CH, Coyaji KJ, Hirve SS, Rao S, et al. (2003) Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. Int J Obes Relat Metab Disord 27: 173-180.
9. No authors listed (2015) Standards of Medical Care in Diabetes-2015. Diabetes Care. 38: S1-S94.
10. Shantha GP, Kumar AA, Kahan S, Cheskin LJ (2012) Association Between Glycosylated Hemoglobin and Intentional Weight Loss in Overweight and Obese Patients With Type 2 Diabetes Mellitus : A Retrospective Cohort Study. The Diabetes Educator 38: 417-426.
11. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, et al. (2009) Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. Endocr Pract 15: 541-559.
12. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, et al. (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 56: 1577-1596.
13. United Kingdom Prospective Diabetes Study Group (1998) United Kingdom Prospective Diabetes Study 24: A 6-Year, Randomized, Controlled Trial Comparing Sulfonylurea, Insulin, and Metformin Therapy in Patients with Newly Diagnosed Type 2 Diabetes That Could Not Be Controlled with Diet Therapy. Ann Intern Med 128: 165-175.
14. American Diabetes Association (2002) Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care. 25: S28-S32.
15. Leibel B (1971) An analysis of the University Group Diabetes Study Program: data results and conslusions. Can Med Assoc J 105: 292-294.
16. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al. (2007) Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. N Engl J Med 357: 28-38.
17. Singh S, Loke YK, Furberg CD (2007) Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care 30: 2148-2153.
18. Nissen SE, Wolski K (2010) Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med 170: 1191-1201.
19. Tanne JH (2007) FDA places "black box" warning on antidiabetes drugs. BMJ 334: 1237.
20. Panikar V (2012) Pioglitazone and bladder cancer: the pros and cons. J Assoc Physicians India 60: 72-73.
21. Chan JC, Gagliardino JJ, Baik SH, Chantelot JM, Ferreira SR, et al. (2009) Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). Diabetes Care 32: 227-233.
22. International Diabetes Federation (2012) Diabetes medication use: international prescription patterns. Belgium.
23. \ http://www.idf.org/diabetesatlas/diabetes-mortality
24. Tripathi BK, Srivastava AK (2006) Diabetes mellitus: complications and therapeutics. Med Sci Monit 12: RA130-147.
25. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, et al. (2011) Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 123: e18-18e209.
26. Lee CM, Huxley RR, Lam TH, Martiniuk AL, Ueshema H, et al. (2007) Prevalence of diabetes mellitus and population attributable fractions for coronary heart disease and stroke mortality in the WHO South-East Asia and Western Pacific regions. Asia Pac J Clin Nutr 16: 187-192.
27. Ringborg A, Cropet C, Jönsson B, Gagliardino JJ, Ramachandran A, et al. (2009) Resource use associated with type 2 diabetes in Asia, Latin America, the Middle East and Africa: results from the International Diabetes Management Practices Study (IDMPS). Int J Clin Pract 63: 997-1007.
28. Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, et al. (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 28: 88-136.
29. Stolar M (2010) Glycemic control and complications in type 2 diabetes mellitus. Am J Med 123: S3-11.
30. American Diabetes Association (2002) Implications of the Diabetes Control and Complications Trial. Diabetes Care. 25: S25-S27.
31. Ceriello A, Ihnat MA, Thorpe JE (2009) Clinical review 2: The "metabolic

memory": is more than just tight glucose control necessary to prevent diabetic complications? J Clin Endocrinol Metab 94: 410-415.

32. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, et al. (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353: 2643-2653.

33. No authors listed (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 329: 977-986.

34. Ranjit Unnikrishnan I, Anjana RM, Mohan V (2011) Importance of controlling diabetes early--the concept of metabolic memory, legacy effect and the case for early insulinisation. J Assoc Physicians India 59 Suppl: 8-12.

35. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359: 1577-1589.

36. Ceriello A (2008) The Hyperglycemia-Induced "Metabolic Memory": The New Challenge for the Prevention of CVD in Diabetes. Rev Esp Cardiol Supl. 8:11C-17C.

37. Zammitt NN, Frier BM (2005) Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 28: 2948-2961.

38. Unger J (2003) Educating patients about hypoglycemia prevention and self-management. Clinical Diabetes 31: 179-188.

39. No authors listed (2001) Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. Diabetes Care 24: 1711-1721.

40. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, et al. (2005) Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. N Engl J Med 353: 2643-2653.

41. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, et al. (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560-2572.

42. Heller SR1; ADVANCE Collaborative Group (2009) A summary of the ADVANCE Trial. Diabetes Care 32 Suppl 2: S357-361.

43. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, et al. (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545-2559.

44. Genuth S, Ismail-Beigi F (2012) Clinical implications of the ACCORD trial. J Clin Endocrinol Metab 97: 41-48.

45. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, et al. (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 355: 2427-2443.

46. Levetan C (2007) Oral antidiabetic agents in type 2 diabetes. Curr Med Res Opin 23: 945-952.

47. Heller S (2008) Sudden death and hypoglycaemia. Diabetic Hypoglycemia 1: 2-7.

48. Lingvay I (2011) Hypoglycemia in Type 2 Diabetes—Consequences and Risk Assessment. US Endocrinology 7: 95-102.

49. Frier BM, Schernthaner G, Heller SR (2011) Hypoglycemia and cardiovascular risks. Diabetes Care 34 Suppl 2: S132-137.

50. Wright RJ, Frier BM (2008) Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev 24: 353-363.

51. Rana O, Byrne CD, Kerr D, Coppini DV, Zouwail S, et al. (2011) Acute hypoglycemia decreases myocardial blood flow reserve in patients with type 1 diabetes mellitus and in healthy humans. Circulation 124: 1548-1556.

52. Khan MI, Barlow RB, Weinstock RS (2011) Acute hypoglycemia decreases central retinal function in the human eye. Vision Res 51: 1623-1626.

53. Cryer PE (2008) The barrier of hypoglycemia in diabetes. Diabetes 57: 3169-3176.

54. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, et al. (2009) The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 339: b4909.

55. Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff DC Jr, et al. (2012) The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care 35: 409-414.

56. UK Hypoglycaemia Study Group (2007) Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.

57. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, et al. (2005) Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabet Med 22: 749-755.

58. Bode BW (2007) Is Weight Gain an Unavoidable Consequence of Insulin Therapy? The Internet Journal of Internal Medicine 6: 2.

59. Ly TT, Gallego PH, Davis EA, Jones TW (2009) Impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes. Diabetes Care 32: 1802-1806.

60. Cryer PE, Davis SN, Shamoon H (2003) Hypoglycemia in diabetes. Diabetes Care 26: 1902-1912.

61. Diabetes Health Center (2015) Diabetes and Morning high blood sugar.

62. Hypoglycemia Support Foundation (2015) Hypoglycemia – A result of gastric bypass surgery.

63. Bailey CJ (2011) The challenge of managing coexistent type 2 diabetes and obesity. BMJ 342: d1996.

64. Eckel RH, Kahn R, Robertson RM, Rizza RA (2006) Preventing Cardiovascular Disease and Diabetes: A Call to Action From the American Diabetes Association and the American Heart Association. Circulation 113: 2943-2946.

65. Banks E, Lim L, Seubsman SA, Bain C, Sleigh A (2011) Relationship of obesity to physical activity, domestic activities, and sedentary behaviors: cross-sectional findings from a national cohort of over 70,000 Thai adults. BMC Public Health 4:762.

66. Ahima RS (2011) Digging deeper into obesity. J Clin Invest 121: 2076-2079.

67. Apovian CM (2011) Management of diabetes across the course of disease: minimizing obesity-associated complications. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 4: 353-369.

68. Pi-Sunyer FX (2009) The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. Postgrad Med 121: 94-107.

69. De Block CE, De Leeuw IH, Van Gaal LF (2005) Impact of overweight on chronic microvascular complications in type 1 diabetic patients. Diabetes Care 28: 1649-1655.

70. Chase HP (2015) Advantages and disadvantages of insulin pumps. UCDenver University, USA.

71. Inzucchi SE, McGuire DK (2008) New drugs for the treatment of diabetes: part II: Incretin-based therapy and beyond. Circulation 117: 574-584.

72. Colagiuri S (2010) Diabesity: therapeutic options. Diabetes Obes Metab 12: 463-473.

73. Dicker D (2011) DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. Diabetes Care 34 Suppl 2: S276-278.

74. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, et al. (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369: 1317-1326.

75. Cobble ME, Frederich R (2012) Saxagliptin for the treatment of type 2 diabetes mellitus: assessing cardiovascular data. Cardiovasc Diabetol 11: 6.

76. Fisman EZ, Tenenbaum A (2009) A cardiologic approach to non-insulin antidiabetic pharmacotherapy in patients with heart disease. Cardiovasc Diabetol 8: 38.

77. Jeon WS, Park CY (2014) Antiobesity pharmacotherapy for patients with type 2 diabetes: focus on long-term management. Endocrinol Metab (Seoul) 29: 410-417.

78. Desouza CV, Bolli GB, Fonseca V (2010) Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 33: 1389-1394.

79. Sesti G (2011) Glycemic control impact on body weight potential to reduce cardiovascular risk: glucagon-like peptide 1 agonists. Diabetes Care 34 Suppl 2: S272-275.

80. Aquilante CL (2010) Sulfonylurea pharmacogenomics in type 2 diabetics:the influence of drug target and diabetes risk polymorphism. Expert Rev Cardiovasc Ther 8: 359-372.

81. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, et al. (2003) Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation 108: 2941-2948.

82. Dailey G, Admane K, Mercier F, Owens D (2010) Relationship of insulin dose, A1c lowering, and weight in type 2 diabetes: comparing insulin glargine and insulin detemir. Diabetes Technol Ther 12: 1019-1027.