Type 2 Diabetes Mellitus- Disease, Diagnosis and Treatment

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Abstract

Type 2 diabetes mellitus (T2DM) is a fast-growing disease and a leading global public health concern. Multiple complications are associated with T2DM. Patient education with lifestyle modifications and pharmacotherapy are main methods for treatment of patients afflicted with T2DM. Lifestyle interventions are effective strategies but usually persist for a short term whereas T2DM patients with long-term treatment still present challenges in many cases. In this review, we have briefly summarized recent progress for T2DM diagnosis and treatment. We attempt to provide an outline for T2DM diagnosis and treatment. In addition, we introduce Chinese herbal medicine as an alternate treatment for physicians and T2DM patients.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder and typically results from excess of caloric intake over energy expenditure. It is characterized by a progressive insulin secretory defect due to insulin resistance, which increases the body's demand for insulin in order to retain glucose homeostasis. If pancreatic β-cells fail to secrete enough insulin to compensate for increasing insulin demand, the blood glucose level will be elevated gradually [1]. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels resulting in increasing levels of morbidity and mortality [2]. T2DM associated with poor lifestyle is a primarily factor leading to the progressive reduction of physical activity and changes of dietary habits. As a consequence, a greater percentage of the population will become overweight and obese. T2DM is the one of the most prevalent chronic diseases worldwide and one of the major public health challenges of the 21st century. The epidemic of T2DM in the United States and the rest of the world continue to grow rapidly; as many as 20 million people in the United States may have the disease [3]. The vast majority of patients with diabetes suffer from T2DM [4].

Diagnosis of T2DM

Diagnostic criteria and common tests

Hyperglycemia is a major symptom in T2DM. Other typical symptoms of T2DM include polyuria, polydipsia, fatigue, weight loss and urine glucose. Diabetes is usually diagnosed based on plasma glucose criteria. The most widely accepted T2DM diagnostic tests are the Fasting Plasma Glucose (FPG) and the Oral Glucose Tolerance Test (OGTT). Both FPG (diagnostic of diabetes at plasma glucose level ≥ 126 mg/dL or 7.0 mmol/L) [5] and 2-hour OGTT (diagnostic of diabetes at plasma glucose level ≥ 200 mg/dL or 11.1 mmol/L) [5] are commonly used diagnostic tests. The advantages of FPG are low cost and the popularity of automated laboratory machines available. Although the OGTT has long been established as one of the diagnostic modalities for diabetes, compared with FPG, it is less practical as a plasma glucose test in clinical settings. In fact, the WHO discouraged the use of the OGTT for the diagnosis of diabetes due to its inconvenience, high cost, and poor reproducibility.

Blood HbA1c

Blood HbA1c is a favorable diagnostic tool for the following reasons. First, HbA1c measurements can be carried out at any time and do not require preparation by tested subjects. Second, its intra-individual biological variability is low, hence with high reproducibility [6]. HbA1c is not influenced by sudden glycemic variations and psychological stress. Third, it reflects the mean blood glucose levels over the last 3 months. Thus, HbA1c can be measured approximately every 3 months to determine whether a patient's targets for glycemic control have been reached and maintained. Fourth, epidemiological analyses have concluded that for every percentage point decrease in HbA1c level, there is a 25% reduction in diabetes-associated deaths, 35% reduction in the risk of microvascular complications and 18% reduction in combined fatal and non-fatal myocardial infarction [7]. In 2010, the American Diabetes Association (ADA) advocated HbA1 as a diagnostic criterion for diabetes [4]. The ADA selected a result of 6.5% as the cutoff value for T2DM diagnosis, assessed by the development of diabetic retinopathy, which increases steeply at ≥ 6.5% [4]. This roughly corresponds to a fasting blood glucose concentration of 100–125 mg/dL, and to a postprandial glucose concentration of 140–199 mg/dL. In 2011, the HbA1c test was endorsed by the WHO as a diabetes diagnostic test, provided that the measurements are performed by standardized HbA1c tests that passed the stringent quality assurance tests [4]. Since then, HbA1c has officially become a diabetes diagnostic criterion. There are drawbacks for HbA1c measurement. It is affected by erythrocyte conditions. For patients suffering from anemia and hemoglobin disorders, results of HbA1c testing are not reliable. In addition, the diagnostic cutoff values of the HbA1c tests seem to depend on demographic, anthropometric, or laboratory measurements. For example, the China Guideline regarding T2DM in 2010 did not recommend the HbA1c test for the diagnosis

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of diabetes due to inconclusive results in the Chinese population and the lack of a standardized HbA1c measurement nationwide. Results of three studies from different population groups in Shanghai [8], Beijing [9] and Qingdao [10], have found different cutoff points of HbA1c for diabetes [11]. Moreover, it is reported that HbA1c fluctuations due to genetic and biological variations coexist with medical complications and assay interference [4].

Treatment of T2DM

Non-pharmacologic treatment

It is well-established that lifestyle plays a crucial role in prevention and treatment of T2DM [12]. The ADA endorses the education of diabetes self-management. This education can help the patient to obtain necessary knowledge and skills for self-care, manage hyperglycemia and possible hypoglycemia, and make lifestyle changes [13]. Primary non-pharmacological interventions mainly include appropriate nutritional diet, regular physical exercise and smoking cessation. Diet and regular exercise from moderate to intense can improve glucose levels in patients with T2DM and those at risk for developing obese and T2DM. Lifestyle intervention is a proven strategy for reducing diabetes incidence [14,15]. Nevertheless, the intervention is considered effective only in the short term but is difficult to adhere to in the long run, thus limiting its effectiveness.

Anti-diabetes pharmacotherapy

The ultimate goal for the pharmacotherapy is to modify disease progression in a manner preventing pathophysiological decline towards β-cell dysfunction and long-term complications associated with hyperglycemia. People should be aware that all anti-diabetic drugs except insulin require some degree of residual pancreatic β-cells to perform function. A single anti-hyperglycemic drug often suffices initially, but a second drug with a different mechanism of action usually is required with the disease progression. In advanced T2DM, insulin intervention may be necessary. For convenience, oral agents are typically the first choice for the treatment of T2DM but oral delivery bears some drawbacks such as frequent dosing, short half life, and low bioavailability. We outline major anti-diabetic drugs for their efficacy, safety and mechanisms of action in the following pages. It is important for both clinicians and patients to obtain a broad understanding of each class of oral agents so as to optimize diabetic control. In addition, despite the availability of many oral anti-diabetic agents, therapeutic efficacy in some of them is offset by side effects such as weight gain and hypoglycemia. Furthermore, treatment with glucose-lowering agents is generally characterized by loss of efficiency over time, due to progressive β-cell dysfunction. Thereby, there is an unceasing requirement for adjustment including agent dose, and/or agent type or a combination of different agents in all stages of the disease.

Metformin: Metformin is one of the oldest but the safest agents used in the treatment of T2DM. Metformin is the first choice of recommended therapy for T2DM according to the International Diabetes Federation Global Guideline for T2DM [13], in agreement with similar guidelines from the ADA, as well as the European Association for the Study of Diabetes (EASD) [Available from URL: http://apps.who.int/trialsearch]. Metformin exerts its effects primarily by reducing hepatic glucose output through inhibition of gluconeogenesis [16] and has a comparatively lesser effect increasing insulin sensitivity. Hence, unlike insulin or sulfonylureas, metformin is primarily an antihyperglycemic agent, rather than a hypoglycemic agent. As a result, metformin does not cause hypoglycemia. In addition, it does not cause weight gain due

to its anorexic effect. Weight gain can worsen the course of the disease in the long run [16,17]. Metformin also modestly reduces plasma triglyceride concentrations resulting from decreased production of very low density lipoprotein [18] and has favorable effects on a number of cardiovascular risk factors such as lipids, body weight, blood pressure and platelet function [19,20]. Therefore, metaformin is particularly suitable for T2DM obese patients with cardiovascular diseases. Another advantage of metformin is the reduction of mortality, as documented in the UKPDS [21]. The most common reported adverse reaction to metformin therapy is gastrointestinal upset including nausea, vomiting, anorexia and diarrhea [17]. Thus, metformin should be started at a low dose at first (500 mg PO bid). Another drawback to metformin is that it cannot be used when kidney function is impaired indicated by a glomerular filtration rate (GFR) lower than 60 mL/min [22].

If metformin is poorly tolerated or the monotherapy results in an HbA1c value that is still elevated for 3 months, then treatment can be amplified with the addition of a second anti-diabetic drug.

Sulfonylureas: Sulfonylurea binds to the sulfonylurea receptor on the surface of the β-cells and inhibits potassium efflux, thus depolarizing the β-cells and facilitating insulin release [23]. Because sulfonylurea acts by stimulating insulin release from β-cells, patients without a sufficient number of β-cells, such as those with later stages of T2DM, do not respond to the medication. An advantage of sulfonylureas is its low cost to patients. Its disadvantage is that sulfonylurea treatment carries a risk of hypoglycemia, especially in elderly patients. In addition, the drug promotes weight gain. Many patients can increase more than 2 kg after initiative medication [17,24]. Furthermore, sulfonylureas are associated with a higher cardiovascular risk than metformin likely due to impairment of endothelial function with increased risk for ischemic complications [25-27]. It is also noteworthy that some patients with an allergy to sulfonamide medications exhibit cross-reactivity with sulfonylureas.

Glinides, nateglinide and replagnide are a new generation of sulfonylureas. They display similar effects as sulfonylreas by binding to the sulfonylurea receptor and inducing depolarization of the β-cells. However, they bind in a different manner to the sulfonylurea receptor. They also have shorter half-lives than sulfonylureas. Therefore, they require more frequent dosing. Glinides may possess a lower propensity towards hypoglycemia.

GLP1 receptor agonists and DPP-4 inhibitors: Glucagon-like peptide 1 (GLP-1) is a 30-amino-acid peptide. It is an incretin hormone produced by ileum and colon, and released into the bloodstream. GLP-1 is released in response to meal ingestion and blood glucose concentration in a harmonized fashion for hormone release [28]. GLP-1 also exerts an anti-diabetic effect by delaying gastric emptying, suppressing glucagon release and increasing glucose-stimulated insulin release. The resulting effect of GLP-1 is to curb postprandial hyperglycemia, but its half-life after secretion into the blood is very short. Thus, two strategies are used to overcome this problem. A) incretin mimetic such as liraglutide, approved by FDA in 2010, is a long acting GLP-1 degradation enzyme analogue for treatment of T2DM. It has a long half-life of 14 h and is resistant to dipeptidyl peptidase-4 (DPP-4) degradation. B). GLP-1 degradation enzyme inhibitors like DPP-4 is the newest class of oral agents for the treatment of T2DM. DPP-4 inhibitors such as vildagliptin, sitagliptin, saxagliptin, linagliptin and alogliptin inhibit the enzymatic degradation of GLP-1. As a consequence, GLP-1 concentration increases, leading to decreased postprandial glucose level [29]. DPP-4 inhibitors and incretin mimetics do not carry a risk of hypoglycemia, as these drugs seldom alter insulin secretion levels during fasting state.

Another major advantage of the DPP-4 inhibitors is to retain body weight when the patient is mal-nourished or under weight. DPP-4 inhibitors are approved for both monotherapy and co-deliver with metformin and thiazolidinediones. DPP-4 inhibitors have gastrointestinal side effects and may cause urticaria [30]. Moreover, cost of DPP-4 inhibitors is high, a major limiting factor for their clinical use.

Likewise, DPP-4 inhibitors can be used for inhibiting Glucose-dependent Insulinotropic Polypeptide (GIP). GIP is a 42-amino-acid peptide derived from ProGIP, a large protein. GIP is secreted by intestinal K cells, present predominantly in the proximal small intestine, in response to luminal presence of ingested fats, carbohydrates and amino acid sources. Fat is the most potent stimulator of GIP secretion [31]. Intact GIP is a potent stimulator of glucose-dependent insulin secretion in healthy humans. After secretion, the two N-terminal amino acids of GIP are cleaved-off by DPP-4 and the hormone is then inactivated. It is reported that the GIP works in synergy with glucose to stimulate β-cell proliferation and improve survival of pancreatic β-cells [32,33].

Thiazolidinediones: Thiazolidinediones (TZDs) including rosiglitazone and pioglitazone are drugs acting as insulin sensitizers. The effects of TZDs are mediated through peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR- receptors are mainly located in the adipocytes, and also distributed in skeletal muscle, liver and the pancreatic β-cells. The TZD-PPAR complex acts on response elements in promoter regions to affect the transcription of many genes. They may stimulate production of proteins that increase insulin sensitivity [34] and block transcription of proteins responsible for insulin resistance or inflammation [35]. In addition to glucose-lowering effects, pioglitazone may also improve lipid profiles, possibly due to its partial PPAR-α activity.

Pioglitazone has a very low risk of hypoglycemia in monotherapy. It can be taken by patients with advanced renal insufficiency. Its disadvantages are weight gain, fluid retention that can worsen cardiac insufficiency, an increased risk of bone fractures, a rare side effect of hepatotoxicity and possibly, an increased incidence of bladder cancer [36,37]. A meta-analysis suggested that patients using rosiglitazone may have an increase in the risk of myocardial infarction and death from cardiovascular causes [38].

SGLT-2 inhibitors: Sodium-glucose co-transporter 2 (SGLT2) inhibitors are another new class of anti-diabetic drug with an insulin-independent mechanism. The SGLT2 is a transporter found in the kidney proximal tubule and is responsible for approximately 90% of renal glucose reabsorption. The SGLT2 inhibitors like dapagliflozin are highly selective SLGT2-inhibitors and reduce reabsorption of glucose in the kidney [39]. As a consequence, glucose excretion increases in the urine, resulting in glycouria, whereas plasma glucose levels decrease in blood, an insulin independent reduction. Thus, SGLT-2 inhibitors do not confer any risk of hypoglycemia. In addition to improvements in glycemic control, dapagliflozin therapy is also associated with a beneficial reduction in total body weight. A disadvantage for SGLT-2 inhibitors is an increased incidence of genital infections.

Alpha-glucosidase inhibitors (AGIs): AGIs such as acarbose, voglibose and miglitol are pseudo-carbohydrates that competitively inhibit α-glucosidase enzymes located in the brush border of small intestine that hydrolyze non-absorbable polysaccharides and oligosaccharides into absorbable monosaccharides [40]. As a result, the effect of these drugs is to retard glucose absorption after a meal, and consequently lowers postprandial insulin levels and hyperglycemia peaks in patients with few β-cell reserves. AGIs are commonly used to control postprandial blood glucose and to reduce the insulin requirement without causing hypoglycemia and weight gain [41]. AGIs can be administered as monotherapy or in combination with any other blood glucose-lowering drug, including insulin for the treatment of T2DM [42]. The primary drawback of α-glucosidase inhibitors is its gastrointestinal disturbance such as flatulence and diarrhea [43].

Strategies for insulin therapy: Insulin therapy was classically considered a last step for T2DM patients and did not use until all other treatments failed. The goals of insulin therapy in T2DM are glycemic and metabolic control to prevent micro- and macrovascular complications. People should be aware if the insulin dose is too high or incorrectly distributed, hypoglycemia and marked weight gain may occur. The treatment begins at a dose of 10 to 20 IU of a long-acting insulin preparation. Depending on the patient's weight, a dose increase by 2 IU every three days may be required until the morning glucose values are within the target range. If glycemic peaks after meals are the main problem, then insulin therapy would more reasonably be initiated with insulin administration only at mealtimes [44].

It is increasingly being recognized that insulin may be used at an early stage of T2DM. Recent treatment guidelines recommend the use of insulin, especially basal insulin, as part of an early treatment regimen in the disease process. The early insulin therapy may slow or even halt diabetes progression. In patients with newly diagnosed T2DM, several small-scale studies have demonstrated that short term intensive insulin treatment can induce disease remission (defined by normal glucose levels) for up to 2 years [45,46]. The ADA and EASD recommend starting insulin treatment with basal insulin based on both the efficacy and relative safety of this approach [47]. Currently available basal insulin analogs, such as insulin glargine (Lantus; Sanofi, Paris, France) and insulin detemir (Levemir; Novo Nordisk Inc, Plainsboro, NJ) offer better improvement in terms of duration of action and reduced peak effect [48].

Bariatric surgery: Bariatric surgery includes Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), laparoscopic adjustable gastric banding (LAGB), biliopancreatic diversion (BPD) and the biliopancreatic diversion with a duodenal switch (BPD-DS). The RYGB and the BPD procedures bypass a full length of normal intestine (bypass procedures) whereas the LAGB and LSG only restrict the normal flow of food (restrictive procedures) [49].

Most T2DM patients are overweight or obese [50]. Patients with T2DM and body mass index (BMI) < 35 kg/m^2 are primarily offered conventional treatment since there has been considerable debate about extending the benefits of bariatric surgery to those patients. The diabetic patients with BMI > 35 kg/m^2 are currently eligible for bariatric surgery, according to the NIH Consensus Criteria for bariatric surgery. Recent meta-analyses of 16 studies with 6131 patients and mean 17.3-month follow-up have found bariatric surgery to be superior to conventional medical therapy in achieving significant weight loss, HbA1c and fasting plasma glucose reduction and diabetes remission [51]. Thus, bariatric surgery has been accepted as the most effective treatment along with significant metabolic benefits for patients with T2DM and BMI > 35 kg/m^2 [52]. Weight loss after surgery is not due to intestinal malabsorption, but due to decreased food consumption from decreased appetite. Evidence exists that changes in the gut hormonal milieu after gastric bypass can improve insulin resistance immediately after surgery and proceed substantial weight loss. The exact mechanisms for diabetes emission remain unknown. There are several hypotheses including the hindgut or incretin theory, the foregut theory and the midgut or

intestinal/hepatic regulation theory [53]. Remission of diabetes is likely to be related to both weight loss and hormonal changes that occur after surgery.

There were several limitations of this analysis. 1). All of these studies were of short durations and involved a relatively small number of patients. Obviously, long-term outcomes are more important to assess the true impact of these interventions as they are used to treat chronic conditions [54]. 2). A considerable portion of the source data were not run on a randomized group of patients, but rather a collection of mainly retrospective reports in the literature. 3). There was a large heterogeneity in the definition of diabetes remission in the literature. Remission of T2DM after bariatric surgery depends on the definition of the remission used for evaluation.

Chinese herbal medicines: As mentioned above, a number of anti-diabetic drugs are effective for T2DM treatment. However, these medications frequently have side effects, such as weight gain, bone loss, and increased risk of cardiovascular events. These side effects could become more prevalent due to continuous treatment of chronic diseases. Herbal medications can be a good alternative in combination with or as a partial replacement for Western medications [55-57]. Because herbal medicines are usually derived from natural plants, they are considered to be relatively safe and have fewer side effects compared to the conventional drugs. Herbal medicine has long been used in China in the treatment of diabetes for several thousands of years and currently it has been intensively used for diabetes treatment. Over 70% of Chinese patients are treated with traditional Chinese herbal medicines [58]. Diabetes is a huge burden in China, where approximately 100 million people have been diagnosed with the disease and the prevalence is 9.7% in China [59]. The application of herbal medicines for diabetic patients is increasing in clinics across the United States. Investigation shows that among people with diabetes, 22.3% of patients use herbal therapy or folk medicine [60]. It is estimated that more than 200 species of plants exhibit hypoglycaemic properties [57]. The investigation shows that about 33 Chinese traditional medicines such as *Radix Astragali seu Hedysari, Radix Rehmanniae* and *Radix Rehmanniae, Praeparata, Radix Trichosanthis,* are most frequently used in Chinese traditional prescriptions for the clinical treatment of diabetes and its complications [61]. Some Chinese anti-diabetic herbs have been proven effective [62] although some research findings are not consistent. Clinical evidence and animal tests show that many Chinese herbs are beneficial in lowering blood glucose and increase insulin sensitivity [63,64]. Mechanism and philosophy of Chinese herbal medicines and Western medicine are different. Unlike Western medicine, which usually contains a single active ingredient, an herb or herbal concoction may contain several active ingredients relaying multiple mechanisms and emphasizing a regulation of the integrated body system. In addition, as plant drugs, therapeutic effects of herbs are weaker than their Western counterparts in lowering blood glucose levels and their side effects. Because of these features, Chinese herbs may be more suitable for prevention and treatment of early stage T2DM and diabetic complications for better therapeutic outcomes [65].

The efficacy and safety of anti-DM herbs are facing challenges. First, experimental evidence regarding active constituents, toxicity, pharmacokinetics and efficacy of Chinese herbs is deficient. Second, herbal medicines are not totally free from side effects and most of the herbs and herb products on the market today have not been subjected to a drug approval process to verify their safety. These herbs have not been well studied using randomized, double-blinded clinical trials, although many animal studies have been carried out [62].

Conclusion

We describe the current understanding of T2DM diagnostic criteria and antidiabetic medications including Chinese herbs. We highlight some issues that should be addressed for clinicians and patients. Although T2DM diagnosis and treatment have been improved in the past decade, current available medicines are not able to completely curb the development of T2DM and its complications. Thus, it is important to develop new drugs with improved safety and efficacy for treatment of T2DM in the future.

References

1. Del Prato S (2009) Role of glucotoxicity and lipotoxicity in the pathophysiology of Type 2 diabetes mellitus and emerging treatment strategies. Diabet Med 26: 1185-1192.

2. Joy SM, Little E, Maruthur NM, Purnell TS, Bridges JF (2013) Patient preferences for the treatment of type 2 diabetes: a scoping review. Pharmacoeconomics 31: 877-892.

3. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, et al. (2006) Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care 29: 1263-1268.

4. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33 Suppl 1: S62-69.

5. American Diabetes Association (2010) Standards of medical care in diabetes--2010. Diabetes Care 33 Suppl 1: S11-61.

6. Lapolla A, Mosca A, Fedele D (2011) The general use of glycated haemoglobin for the diagnosis of diabetes and other categories of glucose intolerance: still a long way to go. Nutr Metab Cardiovasc Dis 21: 467-475.

7. Chin SO, Hwang JK, Rhee SY, Chon S, Hwang YC, et al. (2013) Risk factors for the progression of intima-media thickness of carotid arteries: a 2-year follow-up study in patients with newly diagnosed type 2 diabetes. Diabetes Metab J 37: 365-374.

8. Bao Y, Ma X, Li H, Zhou M, Hu C, et al. (2010) Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey. BMJ 340: c2249.

9. Zhou XH, Ji LN, Luo YY, Zhang XY, Han XY, et al. (2009) Performance of HbA(1c) for detecting newly diagnosed diabetes and pre-diabetes in Chinese communities living in Beijing. Diabet Med 26: 1262-1268.

10. Zhou X, Pang Z, Gao W, Wang S, Zhang L, et al. (2010) Performance of an A1C and fasting capillary blood glucose test for screening newly diagnosed diabetes and pre-diabetes defined by an oral glucose tolerance test in Qingdao, China. Diabetes Care 33: 545-550.

11. Ma H, Gao X, Lin HD, Hu Y, Li XM, et al. (2013) Glycated haemoglobin in diagnosis of diabetes mellitus and pre-diabetes among middle-aged and elderly population: Shanghai Changfeng study. Biomed Environ Sci 26: 155-162.

12. Bi Y, Wang T, Xu M, Xu Y, Li M, et al. (2012) Advanced research on risk factors of type 2 diabetes. Diabetes Metab Res Rev 28 Suppl 2: 32-39.

13. 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). Diabetes Care. 35: 1364 -1379.

14. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, et al. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344: 1343-1350.

15. Chen L, Pei JH, Kuang J, Chen HM, Chen Z, et al. (2015) Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. Metabolism 64: 338-347.

16. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, et al. (2011) Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 57: e1-e47.

17. Gross JL, Kramer CK, Leitão CB, Hawkins N, Viana LV, et al. (2011) Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 154: 672-679.

18. Geerling JJ, Boon MR, van der Zon GC, van den Berg SA, van den Hoek AM, et al. (2014) Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice. Diabetes 63: 880-891.

19. Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, Charles MA (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: a post-hoc analysis of the BIGPRO1 trial. Diabetes Metab 35: 385-391.

20. von Eyben FE (2014) Quality improvement of metabolic control for patients with type 2 diabetes treated at a general hospital: a quantitative open cohort study. J Eval Clin Pract 20: 429-435.

21. Holman R (2007) Metformin as first choice in oral diabetes treatment: the UKPDS experience. Journ Annu Diabetol Hotel Dieu .

22. Shaw JS, Wilmot RL, Kilpatrick ES (2007) Establishing pragmatic estimated GFR thresholds to guide metformin prescribing. Diabet Med 24: 1160-1163.

23. Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JP 4th, Boyd AE 3rd, et al. (1995) Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. Science 268: 423-426.

24. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, et al. (2006) Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 29: 1963-1972.

25. Murata GH, Duckworth WC, Hoffman RM, Wendel CS, Mohler MJ, et al. (2004) Hypoglycemia in type 2 diabetes: a critical review. Biomed Pharmacother 58: 551-559.

26. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, et al. (2010) Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 375: 481-489.

27. Del Prato S, Pulizzi N (2006) The place of sulfonylureas in the therapy for type 2 diabetes mellitus. Metabolism 55: S20-27.

28. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368: 1696-1705.

29. Russell S (2013) Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. Int J Clin Pharm 35: 159-172.

30. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A (2012) Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 344: e1369.

31. Rocca AS, LaGreca J, Kalitsky J, Brubaker PL (2001) Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. Endocrinology 142: 1148-1155.

32. Kim W, Egan JM (2008) The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev 60: 470-512.

33. Freeman JS (2009) Role of the incretin pathway in the pathogenesis of type 2 diabetes mellitus. Cleve Clin J Med 76 Suppl 5: S12-19.

34. Yki-Järvinen H (2004) Thiazolidinediones. N Engl J Med 351: 1106-1118.

35. Chinetti G, Fruchart JC, Staels B (2000) Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res 49: 497-505.

36. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, et al. (2006) Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab 91: 3349-3354.

37. 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.

38. Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356: 2457-2471.

39. Meng W, Ellsworth BA, Nirschl AA, McCann PJ, Patel M, et al. (2008) Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem 51: 1145-1149.

40. Lee SS, Yu S, Withers SG (2003) Detailed dissection of a new mechanism for glycoside cleavage: alpha-,4-glucan lyase. Biochemistry 42: 13081-13090.

41. van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, et al. (2005) Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 28: 154-163.

42. Hanefeld M, Schaper F (2008) Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. Expert Rev Cardiovasc Ther 6: 153-163.

43. Scheen AJ (2003) Is there a role for alpha-glucosidase inhibitors in the prevention of type 2 diabetes mellitus? Drugs 63: 933-951.

44. Meah F, Juneja R2 (2015) Insulin tactics in type 2 diabetes. Med Clin North Am 99: 157-186.

45. Weng J, Li Y, Xu W, Shi L, Zhang Q, et al. (2008) Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 371: 1753-1760.

46. Lovre D, Fonseca V2 (2015) Benefits of timely basal insulin control in patients with type 2 diabetes. J Diabetes Complications 29: 295-301.

47. Sakharova OV, Lleva RR, Dziura JD, Spollett GR, Howell SK, et al. (2012) Effects on post-prandial glucose and AGE precursors from two initial insulin strategies in patients with type 2 diabetes uncontrolled by oral agents. J Diabetes Complications 26: 333-338.

48. Peterson GE (2006) Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. Curr Med Res Opin 22: 2613-2619.

49. Perugini RA, Malkani S (2011) Remission of type 2 diabetes mellitus following bariatric surgery: review of mechanisms and presentation of the concept of 'reversibility'. Curr Opin Endocrinol Diabetes Obes 18: 119-128.

50. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB (2005) Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr 81: 555-563.

51. Ribaric G, Buchwald JN, McGlennon TW (2014) Diabetes and weight in comparative studies of bariatric surgery vs conventional medical therapy: a systematic review and meta-analysis. Obes Surg 24: 437-455.

52. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, et al. (2009) Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 122: 248-256.

53. Maleckas A, Venclauskas L, Wallenius V, Lönroth H, Fändriks L (2015) Surgery in the treatment of type 2 diabetes mellitus. Scand J Surg 104: 40-47.

54. Puzziferri N, Roshek TB 3rd, Mayo HG, Gallagher R, Belle SH, et al. (2014) Long-term follow-up after bariatric surgery: a systematic review. JAMA 312: 934-942.

55. Prabhakar PK, Doble M (2011) Mechanism of action of natural products used in the treatment of diabetes mellitus. Chin J Integr Med 17: 563-574.

56. Yang LX, Liu TH, Huang ZT, Li JE, Wu LL (2011) Research progress on the mechanism of single-Chinese medicinal herbs in treating diabetes mellitus. Chin J Integr Med 17: 235-240.

57. Jia W, Gao W, Tang L (2003) Antidiabetic herbal drugs officially approved in China. Phytother Res 17: 1127-1134.

58. Zhao HL, Tong PC, Chan JC (2006) Traditional Chinese medicine in the treatment of diabetes. Nestle Nutr Workshop Ser Clin Perform Programme 11: 15-25.

59. Yang W, Weng J (2014) Early therapy for type 2 diabetes in China. Lancet Diabetes Endocrinol 2: 992-1002.

60. Garrow D, Egede LE (2006) National patterns and correlates of complementary and alternative medicine use in adults with diabetes. J Altern Complement Med 12: 895-902.

61. Li WL, Zheng HC, Bukuru J, De Kimpe N (2004) Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol 92: 1-21.

62. Wang Z, Wang J, Chan P (2013) Treating type 2 diabetes mellitus with traditional chinese and Indian medicinal herbs. Evid Based Complement Alternat Med 2013: 343594.

63. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS (2003) Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 26: 1277-1294.

64. Wu YC, Hsu JH, Liu IM, Liou SS, Su HC, et al. (2002) Increase of insulin sensitivity in diabetic rats received die-huang-wan, a herbal mixture used in Chinese traditional medicine. Acta Pharmacol Sin 23: 1181-1187.

65. Ceylan-Isik AF, Fliethman RM, Wold LE, Ren J (2008) Herbal and traditional Chinese medicine for the treatment of cardiovascular complications in diabetes mellitus. Curr Diabetes Rev 4: 320-328.