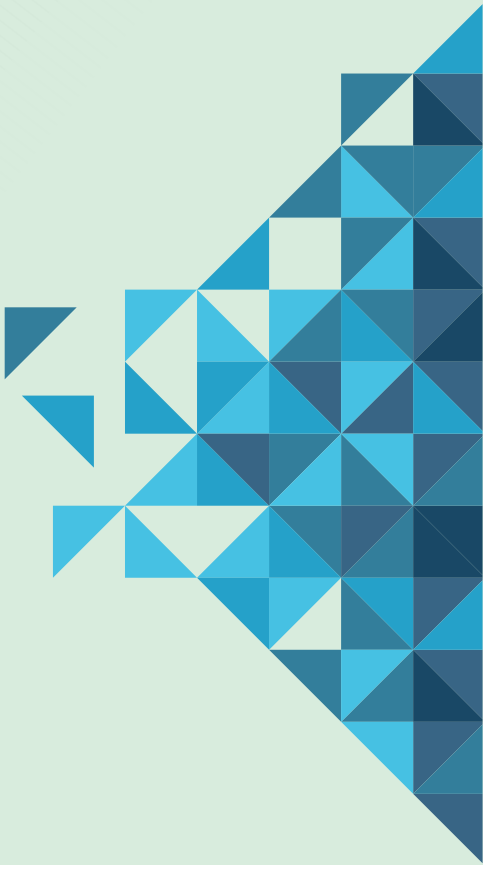
5

LUMINARY LEARNINGS

DIABETES

Continuing Education
Diabetes in India and Southeast Asia

Connect the Dots
Insulin Injection and Blood Glucose Meter Systems



Springer Healthcare Education

In Type 2 Diabetes Uncontrolled on Dual therapy

START EARLY — STEP UP — SYNERGIZE

Glycomet® Trio 1 mg
Metformin HCl 500 mg SR + Glimepiride 1 mg + Voglibose 0.2 mg

Glycomet® Trio 2 mg
Metformin HCl 500 mg SR + Glimepiride 2 mg + Voglibose 0.2 mg

STEP UP

Glycomet® Trio 2 mg/0.3 mg
Metformin HCl 500 mg SR +Glimepiride 2 mg + Voglibose 0.3 mg

In Obese Type 2 Diabetes Uncontrolled on Dual therapy

Glycomet® Trio Forte 2 mg
Metformin HCl 1000 mg SR + Glimepiride 2 mg + Voglibose 0.2 mg

Also Available

Glycomet® Trio Forte 1 mg
Metformin HCl 1000 mg SR + Glimepiride 1 mg + Voglibose 0.2 mg

Glycomet® Trio 1 mg/0.3 mg
Metformin HCl 500 mg SR + Glimepiride 1 mg + Voglibose 0.3 mg

Luminary Learnings

Diabetes

Springer Healthcare Education

July 2019

Springer Healthcare

This edition is created in India for free distribution in India.
This edition is published by Springer Nature India Private Limited.
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
T: +91 11 4575 5888
www.springerhealthcare.com

Part of the Springer Nature group

Contents

Continuing Education

Connect the Dots

1

Diabetes in India and Southeast Asia

Shashank R. Joshi, S. R. Aravind

Epidemiological Trends and Emerging Disease Burden

Diabetes is a multisystem disorder associated with complications, and the prevalence of which is increasing globally. Diabetes imposes immense public health burden with unacceptably high burdens on individuals, their families, and national economies. As the urban–rural divide narrows consistently, it adversely affects the lifestyle of population. The rapid emerging economies of Southeast Asia (SEA) are a victim to the epidemiological transition which results in the shifting of the disease burden from the communicable to the non-communicable diseases. Moreover, Asians have a strong ethnic and genetic predisposition for diabetes and have lower thresholds for the environmental risk factors. There are 387 million people with diabetes in the world with 78.3 million people in the SEA region which is expected to rise to 131 million by the year 2040.

The last three decades have witnessed an epidemic rise in the number of people with diabetes, especially type 2 diabetes, and particularly in developing countries, where more than 80% of the people with diabetes live. The recent landmark study for the pooled analysis across 751 studies with 4.4 million adults from 200 countries published in *Lancet* reflects that between 1980 and

S. R. Joshi, MD, DM, FICP, FACP, FACE, FRCP (✉)
Joshi Clinic, Lilavati & Bhatia Hospital, Mumbai, India
Endocrine Society of India, New Delhi, India
Association of Physicians of India (API) (2014-15), Mumbai, India
Indian Academy of Diabetes, Mumbai, India
RSSDI (Research Society for the Study of Diabetes in India 2011), Mumbai, India
AIAARO (All India Association of Advancement for Research in Obesity), Mumbai, India
e-mail: shashank.sr@gmail.com

S. R. Aravind, MBBS, DNB, FRCP, FDRC, DHA, FRSSDI
Diacon Hospital, Bangalore, India
Columbia Asia Hospital, Yeshwanthpur, Bangalore, India
Post Graduate Studies in Diabetology (RGUHS & RSSDI), Bangalore, India
PESIMSR, Kuppam, India
RSSDI (Research Society for Study of Diabetes in India), Bangalore, India
DiabetesIndia, Hyderabad, India
KRSSDI, Bangalore, India

2014 the number of adults with diabetes in the world increased fourfold from 108 million to 422 million. The increase has particularly been sharp in low- and middle-income countries. In 2014, 50% of adults with diabetes lived in five countries: China, India, the U.S.A., Brazil and Indonesia. The prevalence of diabetes in adults more than doubled for men in India and China (3.7–9.1% in India, 3.5–9.9% in China) but increased by 80% amongst women in India (4.6–8.3%) but only 50% in women in China (5–7.6%). The total number of adults with diabetes in India increased from 11.9 million in 1980 to 64.5 million in 2014. In China, the increase was from 20.4 million in 1980 to 102.9 million in 2014. While India contributed 15.3% of the global share of adults with diabetes in 2014, it was 24.4% for China. Across the region, approximately 72 million people have diabetes – close to one fifth of all adults with diabetes in the world. Overall, the rise of type 2 diabetes in South Asia is estimated to be more than 150% between 2000 and 2035.

Economic and the Societal Impact of the Complications

Diabetes is increasingly affecting individuals in the region in their most productive years (refer to Fig. 1). This will pose a challenge to governments working to improve the economic situation in their countries. The scenario poses huge social and economic problems to most nations in the region and could impede national and, indeed, global development. More than half of the deaths

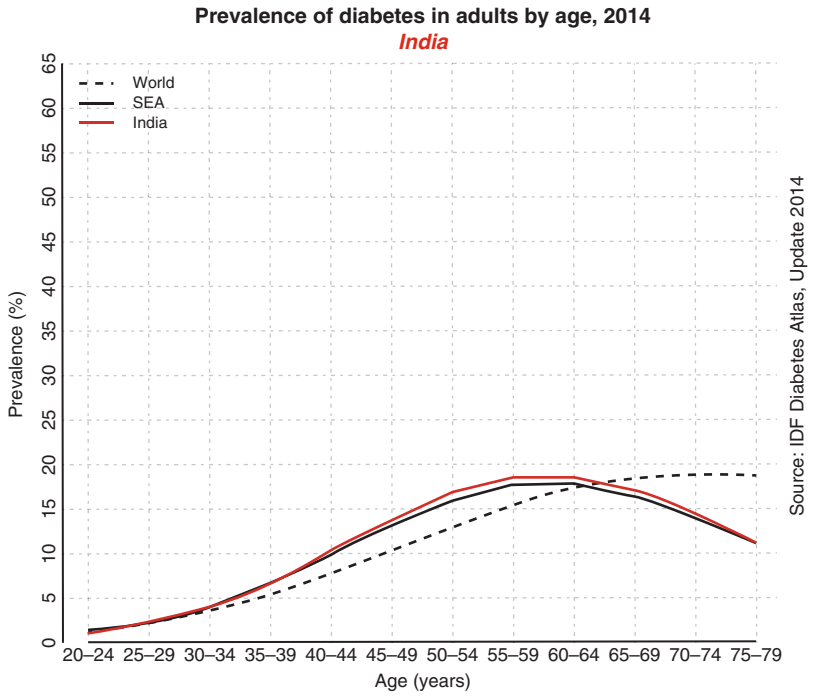


Fig. 1: Age-wise prevalence of diabetes.

due to diabetes occur in people under 60 years of age and one quarter in people under 50 years of age. India is the largest contributor to regional mortality, with 1.1 million deaths attributable to diabetes in 2015. Despite the huge number of people with diabetes in the Southeast Asia Region, health-care spending on diabetes was estimated to be only USD 6 billion, accounting for less than 1% of the global total, with India estimated to have spent the largest proportion. The health-care spending appears to be low as government spending on healthcare is privatised less as predominant healthcare in India. There are an estimated 81,400 children under the age of 15 living with type 1 diabetes in the Southeast Asia region. Approximately 13,100 children developed type 1 diabetes in the region during 2015. India is home to the second largest number of children with type 1 diabetes in the world (70,200), after the U.S.A., and accounts for the majority of the children with type 1 diabetes in the region. More than half (53.2%) of these deaths occurred in people under 60 years of age.

With an estimated 69.2 million people suffering from the condition, the largest in any country in the world, diabetes has become a major healthcare problem in India (refer to Figs. 2 and 3). Recent epidemiological studies from India point to the great burden due to diabetes and its micro- and macrovascular complications. This is primarily because the status of diabetes control in India is far from ideal. Based on the available data, the mean glycated haemoglobin levels are around 9% which is at least 2% higher than the goal currently suggested by International bodies. A balanced approach to improve awareness about diabetes and its control both amongst patients and the medical fraternity is an urgent need of the hour in India.

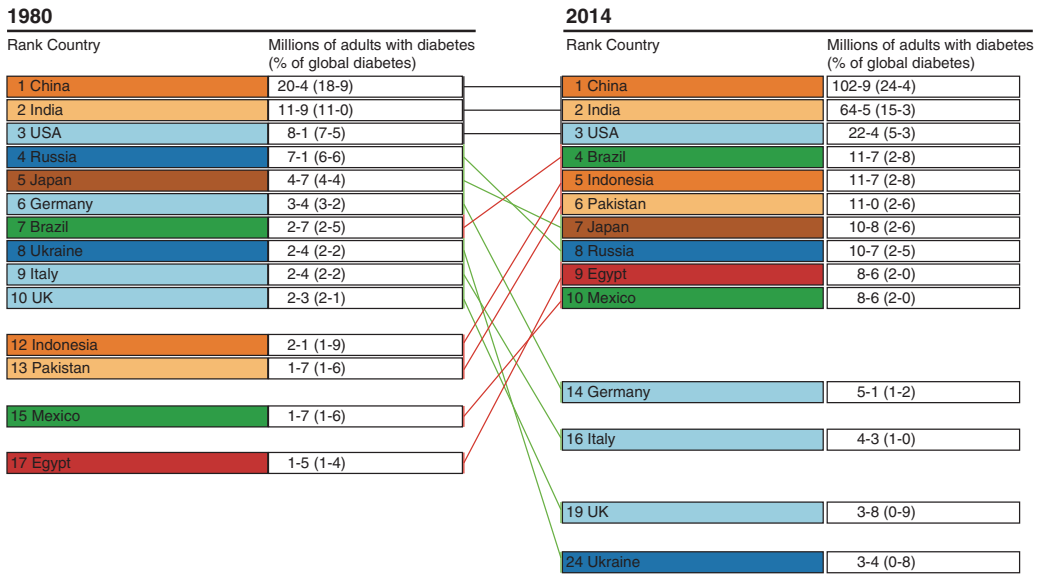


Fig. 2: Ten countries with the largest no. of diabetes in 1980 and 2014 [3].

2015

Rank	Country/territory	Number of people with diabetes
1	China	109.6 million [99.6–133.4]
2	India	69.2 million [56.2–84.8]
3	United States of America	29.3 million [27.6–30.9]
4	Brazil	14.3 million [12.9–15.8]
5	Russian Federation	12.1 million [6.2–17.0]
6	Mexico	11.5 million [6.2–13.7]
7	Indonesia	10.0 million [8.7–10.9]
8	Egypt	7.8 million [3.8–9.0]
9	Japan	7.2 million [6.1–9.6]
10	Bangladesh	7.1 million [5.3–12.0]

Fig. 3: Prevalence of diabetes in different countries (age 20–79 years) [1].

Factors Contributing to the Rapid Increase in Prevalence of Diabetes in Asia

Although ageing, urbanisation and associated lifestyle changes are the major determinants for the rapid increase, an adverse intrauterine environment and the resulting epigenetic changes could also contribute in many developing countries. More action is required to understand the drivers of the epidemic to provide a rationale for prevention strategies to address the rising global public health 'tsunami'.

Urbanisation and Socioeconomic Transition

Diabetes burden in India is contributed by various factors. Genetic predisposition combined with lifestyle changes, associated with urbanisation and globalisation, contributes to this rapid rise of diabetes in India. The highest rates of urbanisation have been in Singapore, Korea, Malaysia, the Philippines and Indonesia (50%). China, Pakistan, India and Thailand have intermediate rates (30%) and Bangladesh and Sri Lanka have slow rates of urbanisation. The increase in urban population and ageing are the main determinants of the global rise in the prevalence of diabetes. Urbanisation and internal rural to urban migration result in several adverse impacts: physical activity decreases, diet habits shift towards high-energy foods and body mass index (BMI) and upper body adiposity increase considerably. The Indian Council of Medical Research (ICMR) study done in the 1970s reported a prevalence of 2.3% in urban areas which has risen to 12–19% in the 2000s. Correspondingly, in rural areas, prevalence rates have increased from around 1 to

4–10% and even 13.2% in one study. Thus it is clear that both in urban and rural India, prevalence rates of diabetes are rising rapidly with a rough urban–rural divide of 2:1 or 3:1 being maintained through the last two to three decades with the exception of Kerala where rural prevalence rates have caught up with or even overtaken urban prevalence rates. The postulates from the ICMR–INDIAB study predicted for the burden of diabetes which projected that in 2011, India would have 62.4 million people with diabetes and 77.2 million people with prediabetes.

Age

As compared to Western population, Asian Indians develop diabetes at a younger age with more prevalence at the age of 60–69 years, whereas in the Chinese population, it peaks at 79–89 years. Indians also have a higher prevalence of impaired glucose tolerance at a younger age than the Chinese population. The findings from Pakistan and Sri Lanka also show similar results.

Anthropometry: Thin-fat Phenotype

It is observed that amongst Asians, diabetes occurs at lower body mass index (BMI) level than in Western population, and small increments in weight trigger glucose intolerance in susceptible subjects. Especially Asian Indians have higher odds of developing diabetes, despite having a significantly lower BMI than the white population.

Several studies in Asian population, particularly in Asian Indians, have highlighted the 'metabolically obese' phenotype amongst normal weight individuals. This phenotype, characterised by greater abdominal obesity despite a normal BMI, less muscle mass, higher percentage of body fat and increased propensity for insulin resistance compared with the Western population, renders higher susceptibility for diabetes in Asian population.

The association of BMI and diabetes is well established and is usually modified by ethnicity. Ethnicity factors that contribute are genetic constitution, lifestyle, living environment and anthropometric characteristics. Body composition related to fat distribution is a stronger determinant of the metabolic milieu than BMI. The diabetes epidemiology, collaborative analysis of diabetes criteria in Europe/in Asia study group noted that the overall effect of age on the prevalence of diabetes differed considerably between the ethnic groups, even in the subjects with the same BMI. Asian population are prone to have more intra-abdominal fat accumulation and low muscle mass. Asian Indians, in particular, have the above abnormalities which account for the high prevalence of insulin resistance and diabetes at low levels of BMI. The risk of diabetes increases progressively from a BMI of ≥23 kg/m^2 amongst Indians. BMI in ≥ of 23 kg/m^2 is also considered overweight for most Asian population. Asian Indians have small body size which has been named as 'thin-fat Indian'. Asian Indians have thinner limbs, which are suggestive of smaller muscle mass. However, despite their thinness, they are centrally obese, with higher waist–hip ratio (WHR) and higher subscapular–triceps skinfold ratio than their British counterparts. Many studies show that Asian Indians have more body fat for any given BMI compared with Caucasians and black Africans. Indians also have higher levels of central obesity (measured as waist circumference [WC], WHR,

visceral fat and posterior subcutaneous abdominal fat). This is reflected in higher plasma non-esterified fatty acid (NEFA) and triglyceride concentrations, hyperinsulinaemia with fasting as well as post-glucose challenge states and higher insulin resistance. Thus, Asian Indians have an unusual thin-fat body composition associated with the insulin resistance syndrome, and this is the now popular 'thin-fat Indian' concept.

Smoking and Alcohol Use

Smoking increases the risk of central obesity and insulin resistance and the risk of diabetes is shown to be higher by 45% in smokers than amongst nonsmokers. The increasing use of alcohol in Asian countries, especially amongst the middle class and rural population, also increases the risk for diabetes and other metabolic diseases and deleterious health effects.

Genetic Susceptibility

The genetic burden on Asian Indians makes the population more susceptible to diabetes. This risk is further increased due to interaction with environmental triggers. Exposure to a high fat diet and lower levels of physical activity trigger the gene–environmental interaction. Both the thrifty genotype and thrifty phenotype hypotheses appear to be the aetiology. The selective presence of 'thrifty genotypes' has been considered to be advantageous in certain population during evolutionary selection by repeated famine and feast cycles. However, these genes have rendered them highly predisposed to obesity and diabetes during the modern era of continuous feasting. On the other hand, the 'thrift phenotype' hypothesis postulates that intrauterine malnutrition leads to metabolic and structural changes in the beta cells that are beneficial for early survival, but increases the risk of T2D and other chronic disorders in adulthood.

Screening

The prevalence of the micro- and macrovascular complications also influences the mortality rate due to diabetes. Unfortunately, more than 50% of individuals with diabetes in India remain undiagnosed, and some may even present with macrovascular disease (coronary artery disease and cerebrovascular disease or stroke and peripheral vascular disease) and microvascular disease (retinopathy, nephropathy and neuropathy) at the time of diagnosis.

Data on various complications of diabetes have also been published by several authors. However, till recently, most of such data were hospital or clinic based and therefore subject to referral bias. The Chennai Urban Rural Epidemiology Study (CURES) and the Chennai Urban Population Study (CUPS) provide the first population-based data from India on virtually all complications of diabetes. CURES was a population-based study involving 26,001 participants aged 20 years or above based on a representative population of Chennai. The overall prevalence of diabetic retinopathy based on four-field stereo colour retinal photography was 17.6%. The

prevalence of overt nephropathy was 2.2% while that of microalbuminuria was 26.9%. Peripheral neuropathy based on biothesiometry was detected in 26.1%.

In the CUPS study, coronary artery disease was evident in 21.4% of diabetic subjects, 14.9% of subjects with impaired glucose tolerance and in 9.1% of people with normal glucose tolerance. In the same study, peripheral vascular disease was present in 6.3% of diabetic subjects compared to 2.7% amongst nondiabetic subjects. Diabetic subjects also had increased subclinical atherosclerosis as measured by intimal-medial thickness at every age point, compared to their nondiabetic counterparts. Assuming that 40 million people in India have diabetes, this translates to at least 7 million with retinopathy, 0.8 million with nephropathy, 10.4 million with neuropathy, 8.5 million with CAD and 2.5 million with PVD. Thus, the burden due to diabetic complications is very high in India due to the sheer number of people with diabetes. These figures are in fact very conservative, and it is possible that in rural areas, the prevalence of complications is much higher because of poorer control of diabetes and lack of access to healthcare.

Identifying accurate and low-cost screening methods is a necessary first step in assessing the cost-effectiveness of screening to detect undiagnosed diabetes. Indian Diabetes Risk Score (IDRS) is more effective and significantly less expensive for screening for undiagnosed T2DM compared to genotyping TCF7L2 SNPs, the strongest genetic marker for T2DM currently available. Using IDRS screening prior to OGTT reduces costs while still detecting a substantial portion of NDD individuals. A potential additional benefit of both the IDRS and genotyping is their ability to identify individuals who currently do not have diabetes but are at high risk of developing diabetes in the future. Thus an individual with an IDRS score of ≥60 at baseline was three times more likely to develop diabetes in the future than low-risk subjects (IDRS <30).

Awareness of Diabetes in India

The awareness of diabetes is a cornerstone of the prevention of this disease. CURES reported that nearly 25% of the population was unaware of diabetes. Only around 40% of the participants felt that the prevalence of diabetes was increasing, and only 22.2% of the population and 41% of known diabetic subjects felt that diabetes could be prevented. Though the awareness levels increased with education, only 42.6% of postgraduates and professionals, which group included doctors and lawyers, knew that diabetes was preventable. The knowledge of risk factors of diabetes was even lower with only 11.9% of the study subjects reporting obesity and physical inactivity as risk factors for diabetes. More alarming was the fact that even amongst known diabetic subjects, only 40.6% were aware that diabetes could lead to some organ damage. There is another population-based study which was done to find out the levels and details regarding awareness on diabetes in urban adult Indian population aged ≥20 years. The knowledge regarding the causes of diabetes, its prevention and the methods to improve the health was significantly low amongst the general population. In the total study group, 41% were unaware of the health being affected by diabetes, and only less than 30% knew about the complications related to kidneys, eyes and nerves. Many persons with diabetes (46%) felt it was a temporary phenomenon. Amongst the diabetic subjects,

92.3% had sought the help of a general practitioner to take treatment. Only a small proportion went to a specialist.

Current Status of Diabetes Control in India

The next challenge in India is that the quality of diabetes care varies considerably depending upon the awareness levels, expertise available, attitudes and perceptions amongst diabetes care providers. An estimate based on sales of antidiabetic pharmaceutical agents shows that on an average only 10–12% of people with diabetes receive modern pharmacological treatment in India. In 1998, the DiabCare–Asia Study was carried out to investigate the relationship between diabetes control, management and late complications in a subset of urban Indian diabetes population treated at 26 tertiary diabetes care centres. A total of 2,269 patients participated in this study and it was observed that approximately half of the patients had poor control (HbA_{1c} >2% points above upper limit of normal), and the mean HbA_{1c} was significantly higher (8.9 ± 2.1%) than the levels recommended by the American Diabetes Association and the ICMR guidelines in India. Over 54% patients had diabetes-related complications. The mean HbA_{1c} levels and frequency of complications were higher in patients with longer diabetes duration. This study also showed that 4% patients were on diet therapy, 53.9% were receiving oral antidiabetic agents (OHAs), 22% were receiving insulin and 19.8% were receiving a combination of insulin and OHAs. This study concluded that with increasing duration of diabetes, glycaemic control deteriorates leading to late complications. It also confirmed that diabetes care in India leaves much to be desired and suggested the need for efforts to increase awareness amongst health professionals to improve diabetes care.

Non-pharmacologic Approach for the Management of Diabetes

Lifestyle modifications are the cornerstone of management of diabetes mellitus and include the prescription of a healthy diet, regular exercise, the management of stress and avoidance of tobacco. The aims of dietary management are to achieve and maintain ideal body weight, euglycaemia and desirable lipid profile, to prevent and postpone complications related to diabetes and to provide optimal nutrition during pregnancy, lactation, growth, old age and associated conditions, e.g. hypertension and catabolic illnesses. Recently published STARCH study shows that Indians consume high carbohydrate in their diet compared to the Western population. The comparison of macronutrients (i.e. region-wise carbohydrate, fat and protein) revealed a similar pattern of dietary consumption, that is, high carbohydrate and a lower range of fat and protein. This study neutralises the myth that only the South Indian population consumes high carbohydrate in their diet (rice, idli, etc.). Dietary transition and a sedentary lifestyle have led to an increase in obesity and diet-related non-communicable diseases like T2DM, cardiovascular disease, etc. predominantly in urban, but also in rural areas. The dietary recommendations should be individualised according to the person's ethnicity, cultural and family background and personal preferences and associated comorbid conditions. It should be flexible in a variety and preparation of food

choices and timing of meals according to the person's daily routine. Both the National Institute of Nutrition and expert group [2] have developed some broad Indian guidelines which recommend reduction intake of carbohydrate, higher intake of fibre, lower intake of saturated fat, optimal ratio of essential fatty acids, slightly higher protein intake, lower intake of salt and restricted intake of sugar.

The role of regular physical activity is well established in the management in persons with type 2 diabetes. A careful assessment of an individual should be made by the physician while incorporating an exercise programme in the management. Exercise programme should be individualised according to the individual capacity and disabilities. The person with diabetes must wear appropriate footwear.

'Clinical Inertia' in Diabetes: Failure to Achieve Tight Control

Failure of initiation of or intensification of therapy, when indicated, is termed 'clinical inertia'. Though we have well-defined management goals, effective therapies and practice guidelines, there is often a failure to take appropriate action despite recognition of the problem. This is a common problem in the management of patients with asymptomatic chronic illnesses. The use of 'soft' reasons to avoid intensification of therapy and lack of education, training and practice organisation aimed at achieving therapeutic goals are the common reasons for clinical inertia. Clinical inertia in achieving glycaemic targets in Indian diabetic subjects could be expected to be even more than in the West, where it has been reported that 65% of the patients diagnosed with diabetes, only 73% are prescribed pharmacologic therapy and only 33% of those treated achieve a haemoglobin A_{1C} value of less than 7% by the ADA goal. This may be due to the low rates of awareness of diabetes and its complications in India resulting in poor glycaemic control seen in Indians with diabetes. Moreover, other factors like poverty, lack of accessibility to health services and inadequate follow-up are additional factors in developing countries like India.

Consequently, insulin is delayed until it is absolutely necessary. Most patients are initiated on insulin after a course of multiple oral antidiabetic drugs. Insulin therapy is initiated only when the HbA_{1c} levels had deteriorated further to around 9%. Physicians often delay insulin therapy worrying that the daily injections, modification of lifestyle due to insulin and dependence on insulin for life and that patients may feel that insulin therapy indicates the last stage of diabetes. However, patients who had moved on to insulin seemed to have a more positive approach towards his/her treatment due to the improvement in quality of life and better control despite the issues outlined above.

Pharmacologic Therapy in Diabetes: is it Different?

A proactive approach to treating type 2 diabetes is recommended: therapy should be individualised with early consideration of combination therapy and ongoing reinforcement of lifestyle modification messages. Indeed, the conservative stepwise approach to type 2 diabetes management involves lifestyle modification, followed by treatment with a single oral antidiabetic agent, often

up-titrated to maximal recommended doses before combination therapy is introduced. Very often there is a delay between stepping up from monotherapy (e.g. metformin alone) to combination therapy (e.g. metformin plus other OADs, often sulphonylurea), and this can result in unacceptable delays in achieving and maintaining glycaemic goals with the potential for long periods of hyperglycaemia. Periods of hyperglycaemia long or even short can increase the risk of micro- and macrovascular complications. The current understanding of the complex pathophysiology of the disease and the progressive deterioration in glycaemic control over time supports the philosophy of earlier intervention with a more comprehensive initial therapy. The major classes of antidiabetic agents that may be combined with metformin include sulphonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitor (DPP4-i), insulin and glucagon-like peptide-1 (GLP-1) receptor agonist. Few studies have investigated the effect of metformin-based early combination therapy. There are several different types of insulin available, but as a minimum, regular quick-acting human insulin and longer-acting NPH insulin should be available to everyone in all parts of the world.

In India, which is a resource-limited country, all therapies are available and it is a predominantly non-reimbursed market. Usually sulphonylureas, metformin, alpha glucosidase inhibitors and glitazone form the cornerstone of therapy with insulin. However, recently gliptins including the low-cost one as well as SGLT2 inhibitors are also available. Biosimilar insulin is also available but not popular and premixed insulin is still used widely. Cost and dose play a role in resource-limited environment. Indian usually requires lower doses and is more insulin resistant.

Translating Primary Prevention of Diabetes

The Indian Diabetes Prevention Programme (IDPP) has been a unique prospective study which has provided several pathways and strategies for the prevention of diabetes in India including the importance of the lifestyle modification and metformin which independently could reduce the incidence of diabetes in Asian Indians with impaired glucose tolerance. Also, these have been proposed as the cost-effective benchmarks amongst high-risk individuals with high degree of insulin resistance and may be useful in other developing countries as well. It is important to control the persistent IGT as it is demonstrated to add to the higher incidence of diabetes with other risk factors for diabetes, such as high BMI, waist circumference and body fat percentage. In a recent collaborative work across South Asia, Latin America and South Africa to compare the prevalence, awareness, treatment and control of diabetes and assess the relationship between diabetes and prediabetes with known cardiovascular and metabolic risk factors, it has been demonstrated that propensity for South Asians to develop diabetes and prediabetes at a younger age and lower body mass index compared with individuals from other low- and middle-income countries. Therefore, it is important that the long-term impact and the complications are prevented, and the health systems and policy makers must make concerted efforts to improve diabetes prevention and detection in the targeted population. Ramachandran A *et al.* have suggested that it is important to develop precise predictors for incident diabetes amongst Asian men. The analysis of the data from the combined cohorts of the Indian Diabetes Prevention Programmes 1 and 2

demonstrates that the baseline HbA (1c) was highly predictive of future diabetes in Asian Indian subjects with impaired glucose tolerance and nearly 60% of the incidence occurred with values ≥6.0. Diagnostic sensitivity of ≥6.5% for new diabetes was only 51% using the oral glucose tolerance test as the standard for comparison. The combination of gamma-glutamyl-transferase (GGT) and fasting plasma glucose (FPG) offers a simple and sensitive tool to identify subjects at high risk of developing diabetes. Similarly, several other markers including adiponectin, IL-6, retinol-binding protein 4, and hypertriglyceridaemic waist phenotype have been proposed to independently associate with incident diabetes. Prospective, intervention studies have demonstrated that increased compliance to lifestyle goals especially with the modification of the diet habits, independent of the physical activity, could result in the decrease in the incident of prediabetes. The mechanistic insights now ascribe these benefits through improvement in insulin sensitivity and beta-cell preservation. Prospective, parallel-group, randomised controlled trial across close to 9,000 subjects have demonstrated that mobile phone messaging is an effective and acceptable method to deliver advice and support towards lifestyle modification to prevent type 2 diabetes in men at high risk. Evidence from the DPP, and other prevention trials conducted in patients with prediabetes, shows that appropriate lifestyle modification including physical activity could lead to risk reduction in the incidence of T2DM by almost 58%. Studies have shown that resistance and aerobic exercise is effective in improving metabolic profile of adults with T2DM. Previous research has reported improved insulin sensitivity/resistance and reductions in hyperglycaemia-related medications as a result of exercise training. In particular, supervised resistance training (max. ten repetitions for >3 days per week) has been shown to lead to significant improvement in insulin sensitivity and values of glycosylated haemoglobin, lipid profile and truncal and peripheral subcutaneous adipose tissue in Asian Indians with T2DM. It has been reported that children and adolescents with type 1 diabetes should complete a minimum of 30–60 min of moderate-intensity physical activity daily. Additional physical activity beyond 60 min/day would be helpful in maintaining glycaemic profile for T2DM patients. The practice of yoga is a traditional Indian practice that helps therapeutically and promotes physical and mental health. Yoga-based lifestyle modification programme helps in the reduction of blood glucose, HbA_{1c}, triglycerides, total cholesterol and VLDL. Mindfulness eating and yoga exercise had health benefits on glycaemic control in pregnant women with GDM in some studies. Yogic exercises have enhanced the antioxidant defence mechanism in diabetics by reducing oxidative stress. Unless drastic steps are taken through national prevention programmes to curb the escalating trends in all of the countries, the social, economic and health-care challenges are likely to be insurmountable.

Organising and Conducting Diabetes Research in the Region

Research Society for the Study of Diabetes in India (RSSDI) is the largest organisation of diabetes health-care professionals and researchers in Asia, which was formed in 1972. Currently, there are more than 5,500 life members from across the country representing 29 Indian states and Union territories. Every year, RSSDI organises the national annual meeting, which not only provides a platform for its members to listen to the leaders in the field of diabetes from within the country as

well as from abroad but also to interact amongst themselves and exchange knowledge and ideas. Annual meetings of RSSDI have been a regular feature for more than four decades and are very well attended. RSSDI has a nationwide presence through its 14 state chapters. All state chapters carry on the work of RSSDI at the state and local level. In addition, these chapters carry out independent activities including CMEs for member physicians, local research grants and awareness programmes for public as well as diabetes patients. RSSDI regularly publishes a newsletter, both in print and electronic format, which serves as an important link between the national body and its membership to keep the members informed of various activities, research grants and educational initiatives. The *International Journal of Diabetes in Developing Countries* (IJDDC) is the prestigious indexed publication of RSSDI and is an important resource of research work done in the field of diabetes in India. RSSDI funds research proposals from Indian scientists interested in conducting research in the field of diabetes mellitus. For providing research grants, RSSDI invites proposals from Indian scientists interested in conducting original research in the field of diabetes mellitus. Furthermore, limited grants are also available for the students of medical colleges for smaller projects. Recently, RSSDI has developed a simple user-friendly novel approach to decide the appropriate antidiabetic agent to be used in type 2 diabetes through the 'therapeutic wheel'. The best choices can be determined from the outer rings of the wheel (orange and red), and the choices can be further streamlined by an 'individualised approach' (Fig. 4).

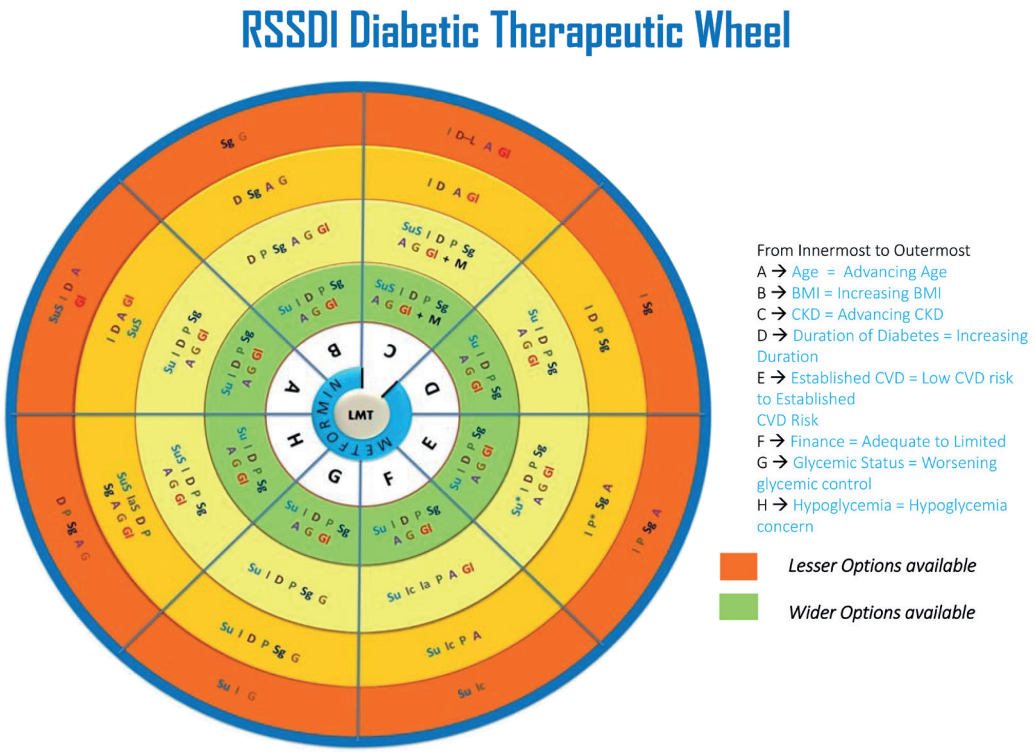


Fig. 4: The RSSDI therapeutic wheel.

Future Directions: Unmet Needs, Unanswered Questions and Unquestioned Answers

There have been rapid epidemiological transitions translating into a huge disease burden in diabetes in the SEA region. Prevention of diabetes through consistent awareness about the disease in population would be a critical step forward which would have tremendous implications that halt the progress of disease. One of the global targets for noncommunicable disease is to halt by 2025 the rise in the prevalence of diabetes to its 2010 levels. A better understanding for the basis for the gene–environment interaction, in which beta-cell dysfunction, typically on the background of insulin resistance, is critical for the increase in glucose levels observed in impaired glucose metabolism and for the development of the hyperglycaemia of type 2 diabetes, would be explored to target effective therapies. Prevention is of utmost importance, but for the more than 420 million people currently living with diabetes, managing their disease must remain the priority. The recent WHO's report recommends a multidisciplinary approach with patient education, medication and consistent follow-up. For primary prevention, the challenge lies in raising awareness, promoting health literacy and identifying individuals at high risk of diabetes for early intervention. For secondary prevention, poor access to care, clinical inertia and treatment non-adherence are major barriers in evidence-based practice. Given the phenotypic heterogeneity of diabetes, and thus the pluralistic needs of those affected, clinical acumen to identify problems and sufficient contact time to empower the person to change behaviour and adhere to treatment are key to successful management.

Screening in young-onset diabetes in India for CV risk factors and complications would be vital to curb the impact of the microvascular and macrovascular complications. This has been clearly demonstrated in the landmark CINDI and CINDI 2 trials published recently for the clinic-based survey amongst 4,600 patients for diabetes-related complications and a retrospective cross-sectional study of 1,500 patients with newly detected young-onset diabetes, respectively.

Conclusions

Considering the enormous burden due to diabetes in India, it is important to realise the cost-effective measures of diabetes care like early screening, tight metabolic control, monitoring of risk factors and assessing of the organ damage. The study done for economic analysis in diabetes care in India has also shown that the cost of providing routine care is only a fraction of the overall cost and is perhaps still manageable. However, when this is not available or its quality is poor, the overall direct and indirect costs escalate with disastrous health and economic consequences to the individual, his family and society particularly due to the onset of the micro- and macrovascular complications of diabetes. Published data from several epidemiological, experimental human and animal studies as well as the data from several megatrials have convincingly proved the importance of tight metabolic control in arresting and preventing the progression of target organ damage. In the last two decades, there is a better understanding of the pathophysiology of type 2 diabetes and availability of newer oral drugs for diabetes; newer insulin and improved delivery systems

should translate to improve diabetes control. However, the survey described above indicates the gaps between the guidelines and real-life practice. In view of this, appreciation and understanding of both patient and physician barriers regarding proper monitoring and judicious use of therapeutic options including insulin therapy for optimising diabetes management should be encouraged in order to improve control of diabetes in India. Result-oriented organised programmes involving patient education, updating medical fraternity on various developments in the management of diabetes and providing them the opportunity to use and analyse these newer treatment options in the form of observational studies are required to combat the diabetes epidemic currently threatening to affect the lives of millions of people in India. Coordination, patient education and ongoing support are important components of quality diabetes care, but most health-care systems are created to provide acute and episodic care rather than chronic care. The effectiveness of team-based chronic care management is well established but not widely implemented. Thus, the challenge lies in designing alternative care models that identify people with undetected diabetes, define individual needs, provide interdisciplinary care and measure effectiveness to make diabetes prevention and control programmes accessible, affordable and sustainable. It is time to evaluate existing policies to address diabetes and devise a strategy and accountability framework for short-, medium- and long-term solutions to address the growing unmet needs in diabetes prevention and control. Immediate action is needed to avert this escalating health disaster.

References

1. International Diabetes Federation. Diabetes Atlas. 7th ed. 2015 Update. http://www.diabetesatlas.org/resources/2015-atlas.html. Last accessed on 21 Apr 2016.
2. Misra A, Sharma R, Gulati S. Consensus dietary guidelines for healthy living and prevention of obesity, the metabolic syndrome, diabetes, and related disorders in Asian Indians. Dia Tec Ther. 2011;13(6):683–94.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet. 2016;387:1513–30.

Further Reading

4. Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance in India. In: Gan D, editor. Diabetes atlas. Belgium: International Diabetes Federation; 2006. p. 15–103.
5. Mohan V, Sandeep S, Deepa R, *et al*. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125:217–30.
6. Mohan V, Alberti KGMM. Diabetes in the tropics. In: Alberti KGMM, Zimmet P, Defronzo RA, *et al*., editors. International text book of diabetes mellitus. 2nd ed. Chichester: Wiley; 1997. p. 171–87.
7. Nakagami T, Qiao Q, Carstensen B, The DECODE-DECODA Study Group, *et al*. Age, body mass index and type 2 diabetes-associations modified by ethnicity. Diabetologia. 2003;46:1063–70.
8. Banerji MA, Faridi N, Atluri R, *et al*. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. J Clin Endocrinol Metab. 1999;84:137–44.
9. Zargar AH, Wani AI, Masoodi SR, *et al*. Mortality in diabetes mellitus—data from a developing region of the world. Diabetes Res Clin Pract. 1999;43:67–74.
10. Mohan V, Shanthirani CS, Deepa M, *et al*. Mortality rates due to diabetes in a selected urban south Indian population – the Chennai Urban Population Study (CUPS-16). J Assoc Phys India. 2006;54:113–7.
11. Rema M, Deepa R, Mohan V. Prevalence of retinopathy at diagnosis among type 2 diabetic patients attending a diabetic centre in South India. Br J Ophthalmol. 2000;84:1058–60.
12. Ramachandran A, Snehalatha C, Satyavani K, *et al*. Prevalence of vascular complications and their risk factors in type 2 diabetes. J Assoc Physicians India. 1999;47:1152–6.

13. Tripathy BB, Panda NC, Tej SC, *et al*. Survey for detection of glycosuria, hyperglycaemia and diabetes mellitus in urban and rural areas of Cuttack district. J Assoc Physicians India. 1971;19:681.
14. Ahuja MMS, Sivaji L, Garg VK, *et al*. Prevalence of diabetes in northern India (Delhi area). Horn Metab Res. 1974;4:321.
15. Gupta OP, Joshi MH, Dave SK. Prevalence of diabetes in India. Adv Metab Disord. 1978;9:147–65.
16. Murthy PD, Pullaiah B, Rao KV. Survey for detection of hyperglycaemia and diabetes mellitus in Tenali. In: Bajaj JS, editor. Diabetes mellitus in developing countries. New Delhi: Interprint; 1984. p. 55.
17. Patel JC. Prevalence of hypertension and diabetes mellitus in a rural village. J Diabet Assoc India. 1986;26:68.
18. Ramachandran A, Jali MV, Mohan V, *et al*. High prevalence of diabetes in an urban population in South India. Br Med J. 1988;297:587–90.
19. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev. 2002;3:141–6.
20. Rao PV, Ushabala P, Seshiah. The Eluru survey: prevalence of known diabetes in a rural Indian population. Diabetes Res Clin Pract. 1989;7:29–31.
21. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet. 1991;337:382–6.
22. Wander GS, Khurana SB, Gulati R, *et al*. Epidemiology of coronary heart disease and risk factors in a rural Punjab population: prevalence and correlation with various risk factors. Ind Heart J. 1994;46:319–23.
23. Ramachandran A, Snehalatha C, Dharmaraj D, *et al*. Prevalence of glucose intolerance in Asian Indians. Urban–rural difference and significance of upper body adiposity. Diabetes Care. 1992;15:1348.
24. Ramankutty V, Joseph A, Soman CR. High prevalence of type 2 diabetes in an urban settlement in Kerala, India. Ethn Health Med. 1999;4:231–9.
25. Zargar AH, Khan AK, Masoodi SR, *et al*. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in the Kashmir Valley of the Indian subcontinent. Diabetes Res Clin Pract. 2000;47:135.
26. Ramachandran A, Snehalatha C, Kapur A, Diabetes Epidemiology Study Group in India (DESI), *et al*. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001;44:1094.
27. Misra A, Pandey RM, Devi JR, *et al*. High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India. Int J Obes. 2001;25:1722–9.
28. Mohan V, Shanthirani CS, Deepa R. Glucose intolerance (Diabetes and IGT) in a selected South Indian population with special reference to family history, obesity and lifestyle factors-the Chennai Urban Population Study (CUPS 14). J Assoc Physicians India. 2003;51:771.
29. Sadikot SM, Nigam A, Das S, *et al*. The burden of diabetes and impaired glucose tolerance in India using the WHO 1999 criteria: prevalence of diabetes in India study (PODIS). Diabetes Res Clin Pract. 2004;66:301–7.
30. Gupta A, Gupta R, Sarna M, *et al*. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. Diabetes Res Clin Pract. 2003;61:69.
31. Agrawal RP, Singh G, Nayak KC, *et al*. Prevalence of diabetes in camel milk consuming 'RAICA' Rural Community of North West Rajasthan. Int J Diabetes Dev Countries. 2004;24:109–14.
32. Ramachandran A, Snehalatha C, Baskar AD, *et al*. Temporal changes in prevalence of diabetes and impaired glucose tolerance associated with lifestyle transition occurring in the rural population in India. Diabetologia. 2004;47:860–5.
33. Mohan V, Deepa M, Deepa R, *et al*. Secular trends in the prevalence of diabetes and glucose tolerance in urban South India-the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia. 2006;49:1175.
34. Basavanagowdappa H, Prabhakar AK, Prasannaraj P, Gurudev KC, Virupaksha S. Study of prevalence of diabetes mellitus and impaired fasting glucose in a rural population. Int J Diabetes Dev Countries. 2005;25:98–101.
35. Prabhakaran D, Shah P, Chaturvedi V, *et al*. Cardiovascular risk factor prevalence among men in a large industry of northern India. Natl Med J India. 2005;18:59–65.
36. Reddy KS, Prabhakaran D, Chaturvedi V, on behalf of the Sentinel Surveillance System for Indian Industrial Populations Study Group, *et al*. Methods for establishing a surveillance system for cardiovascular diseases in Indian industrial populations. Bull WHO. 2006;84:461–9.
37. Deo SS, Zantye A, Mokal R, *et al*. To identify the risk factors for high prevalence of diabetes and impaired glucose tolerance in Indian rural population. Int J Diabetes Dev Countries. 2006;26:19–23.
38. Menon VU, Kumar KV, Gilchrist A, *et al*. Prevalence of known and undetected diabetes and associated risk factors in central Kerala – ADEPS. Diabetes Res Clin Pract. 2006;74:289.
39. Chow CK, Raju PK, Raju R, *et al*. The prevalence and management of diabetes in rural India. Diabetes Care. 2006;29:1717–8.

40. Raghupathy P, Antonisamy B, Fall CH, *et al*. High prevalence of glucose intolerance even among young adults in south India. Diabetes Res Clin Pract. 2007;77:269–79.
41. Mohan V, Mathur P, Deepa R, *et al*. Urban rural differences in prevalence of self reported diabetes in India-The WHO-ICMR Indian NCD risk factor surveillance. Diabetes Res Clin Pract. 2008;80:159–68.
42. Ramachandran A, Mary S, Yamuna A, *et al*. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care. 2008;31:893–8.
43. Rema M, Ponnaiya M, Mohan V. Prevalence of retinopathy in non insulin dependent diabetes mellitus in southern India. Diabetes Res Clin Pract. 1996;24:29–36.
44. Dandona L, Dandona R, Naduvilath TJ, *et al*. Population based assessment of diabetic retinopathy in an urban population in southern India. Br J Ophthalmol. 1999;83:937–40.
45. Narendran V, John RK, Raghuram A, *et al*. Diabetic retinopathy among self reported diabetics in southern India: a population based assessment. Br J Ophthalmol. 2002;86:1014–8.
46. Rema M, Premkumar S, Anitha B, *et al*. Prevalence of diabetic retinopathy in Urban India: the Chennai Urban Rural Epidemiology Study (CURES) Eye Study-1. Invest Ophthalmol Vis Sci. 2005;46:2328–33.
47. John L, Sundar Rao PSS, Kanagasabhapathy AS. Prevalence of diabetic nephropathy in non insulin dependant diabetes mellitus. Indian J Med Res. 1991;94:24–9.
48. Gupta DK, Verma LK, Khosla PK, *et al*. The prevalence of microalbuminuria in diabetes: a study from north India. Diabetes Res Clin Pract. 1991;12:125–8.
49. Yajnik CS, Naik SS, Raut KN, *et al*. Urinary albumin excretion rate (AER) in newly-diagnosed type 2 Indian diabetic patients is associated with central obesity and hyperglycaemia. Diabetes Res Clin Pract. 1992;17:55–60.
50. Vijay V, Snehalatha C, Ramachandran A, *et al*. Prevalence of proteinuria in non-insulin dependent diabetes. J Assoc Physicians India. 1994;42:792–4.
51. Mohan V, Meera R, Premalatha G, *et al*. Frequency of proteinuria in type 2 diabetes mellitus seen at a diabetes centre in Southern India. Postgrad Med J. 2000;76:569–73.
52. Varghese A, Deepa R, Rema M, *et al*. Prevalence of microalbuminuria in type 2 diabetes mellitus at a diabetes centre in Southern India. Postgrad Med J. 2001;77:399–402.
53. Ranjit Unnikrishnan I, Rema M, Pradeepa R, *et al*. Prevalence and risk factors of diabetic nephropathy in an Urban South Indian population. The Chennai Urban Rural Epidemiology Study (CURES-45). Diabetes Care. 2007;30(8):2019–24.
54. Mohan V, Premalatha G, Sastry NG. Ischaemic heart disease in south Indian NIDDM patients – a clinic based study on 6597 NIDDM patients. Int J Diabetes Dev Countries. 1995;15:64–7.
55. Ramachandran A, Snehalatha C, Latha E, *et al*. Clustering of cardiovascular risk factors in urban Asian Indians. Diabetes Care. 1998;21:967–71.
56. Mohan V, Deepa R, Shanthirani CS, *et al*. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India. J Am Coll Cardiol. 2001;38:682–7.
57. Premalatha G, Shanthirani CS, Deepa R, *et al*. Prevalence and risk factors of peripheral vascular disease in a selected south Indian population – the Chennai Urban Population Study (CUPS). Diabetes Care. 2000;23:1295–300.
58. Ashok S, Ramu M, Deepa R, *et al*. Prevalence of neuropathy in type 2 diabetic patients attending a diabetes centre in south India. J Assoc Physicians India. 2002;50:546–50.
59. Pradeepa R, Rema M, Vignesh J, *et al*. Prevalence and risk factors for diabetic neuropathy in an urban south Indian population: the Chennai Urban Rural Epidemiology Study (CURES-55). Diabet Med. 2008;25:407–12.
60. Mohan V, Ravikumar R, Shanthirani S, *et al*. Intimal medial thickness of the carotid artery in south Indian diabetic and non diabetic subjects: the Chennai Urban Population Study (CUPS). Diabetologia. 2000;43:494–9.
61. Deepa M, Deepa R, Shanthirani CS, *et al*. Awareness and knowledge of diabetes in Chennai— the Chennai Urban Rural Epidemiology Study [CURES-9]. J Assoc Physicians India. 2005;53:283–7.
62. Murugesan N, Snehalatha C, Shobhana R, *et al*. Awareness, about diabetes and its complications in the general and diabetic population in a city in southern India. Diabetes Res Clin Pract. 2007;77:433–7.
63. Kapur A, Shishoo S, Ahuja MMS, *et al*. Diabetes care in India: patient's perceptions attitudes and practices (DIPPAP-1 study). Int J Diabetes Dev Countries. 1997;17:2–12.
64. Raheja BS, Kapur A, Bhoraskar A, *et al*. DiabCare Asia—India Study: diabetes care in India—current status. J Assoc Physicians India. 2001;49:717–22.
65. American Diabetes Association (ADA) Recommendations Regarding Glycated Hemoglobin Standardization. American diabetes association position statement. Tests of glycemia in diabetes. Diabetes Care. 2004;27:S91–3.
66. Dilley J, Ganesan A, Deepa R, *et al*. Association of A1C with cardiovascular disease and metabolic syndrome in Asian Indians with normal glucose tolerance. Diabetes Care. 2007;30:1527–32.
67. Phillips LS, Branch WT, Cook CB, *et al*. Clin Inertia Ann Intern Med. 2001;135:825–34.

68. Couzin J. Clinical research: deaths in diabetes trial challenge a long-held theory. Science. 2008;884–885:15.
69. Kapur A. Economic analysis of diabetes care. Indian J Med Res. 2007;125:473–82.
70. Nagpal J, Bhartia A. Quality of diabetes care in the middle and high-income group populace: the Delhi Diabetes Community (DEDICOM) survey. Diabetes Care. 2006;29:2341–8.
71. Kapur A, Shishoo S, Ahuja MMS, *et al*. Diabetes care in India: physicians perceptions, attitudes and practices. Int J Diabetes Dev Countries. 1998;18:124–30. 72.
72. Chuang LM, Tsai ST, Huang BY, Tai TY. The status of diabetes control in Asia—a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med. 2002;19:978–85.
73. Mohan V, Goldhaber-Fiebert JD, Radha V, *et al*. Screening with OGTT alone or in combination with the Indian diabetes risk score or genotyping of TCF7L2 to detect undiagnosed type 2 diabetes in Asian Indians. Indian J Med Res. 2011;133:294–9.
74. Engelgau MM, Narayan KMV, Herman WH. Screening for type 2 diabetes. Diabetes Care. 2000;23(10):1563–80.
75. Joshi SR, Das AK, Vijay VJ, Mohan V. Challenges in diabetes care in India: sheer numbers, lack of awareness and inadequate control. J Assoc Physicians India. 2008;56:443–50.
76. Misra A, Nigam P, Hills AP, *et al*. Consensus physical activity guidelines for Asian Indians. Diabetes Technol Ther. 2012;14(1):83–98.
77. Cuff DJ, Meneilly GS, Martin A, *et al*. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. Diabetes Care. 2003;26(11):2977–82.
78. Ishii T, Yamakita T, Sato T, *et al*. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. Diabetes Care. 1998;21(8):1353–5.
79. Silverstein J, Klingensmith G, Copeland K, *et al*. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28(1):186–212.
80. Joshi SR, Bhansali A, Bajaj S, *et al*. Results from a dietary survey in an Indian T2DM population: a STARCH study. BMJ Open. 2014;4(10):e005138.
81. Sadikot SM, Nigam A, Das S, *et al*. Diabetes India. The burden of diabetes and impaired fasting glucose in India using the ADA1997 criteria: prevalence of diabetes in India study (PODIS). Diabetes Res Clin Pract. 2004;66:293–30.
82. Research India Diabetes(ICMR-INDAB) study (phase I): Indian Council of Medical Research India Diabetes 4. Indian J Endocrinol Metab. 2014;18:379–85.
83. The Diabetes Prevention Program Research Group. The diabetes prevention program. Diabetes Care. 2002;25:2165–71.
84. Lindstorm J, Louheranta A, Mannelin M, *et al*. The Finnish diabetes prevention study. Diabetes Care. 2003;26: 3230–6.
85. Misra A, Alappan NK, Vikram N. Effect of supervised progressive resistance-exercise training protocol on insulin sensitivity, glycemia, lipids, and body composition in Asian Indians with type 2 diabetes. Diabetes Care. 2008;31(7):1282–7.
86. Thangasami SR, Chandani AL, Thangasami S. Emphasis of yoga in the management of diabetes. J Diabetes Metab. 2015;6:10.
87. Youngwanichsetha S, Phumdoung S, Inqkathawornwong T. The effects of mindfulness eating and yoga exercise on blood sugar levels of pregnant women with gestational diabetes mellitus. Appl Nurs Res. 2014;27(4):227–30.
88. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
89. Okhubo Y, Hideki K, Araki E, *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus. A randomized prospective six year study. Diabetes Res Clin Pract. 1995;28:103–17.
90. UKPDS Study Group. Intensive blood glucose control with SU and insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. (UKPDS 33). Lancet. 1998;352:837–53.
91. Pung OJ, Sobieraj DM, Engel SS. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2014;16(5):410–7.
92. Screening for Diabetes. American diabetes association. Diabetes Care. 2002;25(1):s21–4.
93. Sosale B, Sosale AR, Mohan AR. (CINDI 2). Cardiovascular risk factors, micro and macrovascular complications at diagnosis in patients with young onset type 2 diabetes in India: CINDI 2. Indian J Endocrinol Metab. 2016;20(1): 114–8.
94. Sosale A, Prasanna Kumar KM, Sadikot SM. (CINDI). Chronic complications in newly diagnosed patients with Type 2 diabetes mellitus in India. Indian J Endocrinol Metab. 2014;18(3):355–60.
95. Krug EG. Trends in diabetes: sounding the alarm. Lancet. 2016;387:1485–6.

96. Madhu SV, *et al*. Guideline development group. Int J Diabetes Dev Countries. 2015;35 Suppl 1:S1–71.
97. Nanditha A, *et al*. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care. 2016;39(3):472–85.
98. Shen J, Prabhakaran D, Tandon N, *et al*. A multiethnic study of pre-diabetes and diabetes in LMIC. Glob Heart. 2016;11(1):61–70.
99. Ramachandran A, *et al*. Combining fasting plasma glucose with gamma-glutamyl transferase improves the sensitivity to predict incident diabetes in Asian Indian men with impaired glucose tolerance. J Assoc Physicians India. 2014;62(11):18–22.
100. Vinitha R, Johnston DG, Ramachandran A, *et al*. Adiponectin, leptin, interleukin-6 and HbA1c in the prediction of incident type 2 diabetes: a nested casecontrol study in Asian Indian men with impaired glucose tolerance. Diabetes Res Clin Pract. 2015;109(2): 340–6.
101. Ram J, Snehalatha C, Ramachandran A, *et al*. Retinol binding protein-4 predicts incident diabetes in Asian Indian men with prediabetes. Biofactors. 2015;41(3):160–5.
102. Ramachandran A, *et al*. Improvement in diet habits, independent of physical activity helps to reduce incident diabetes among prediabetic Asian Indian men. Diabetes Res Clin Pract. 2014;106(3):491–5.
103. Ramachandran A, *et al*. Hypertriglyceridaemic waist phenotype as a simple predictive marker of incident diabetes in Asian-Indian men with prediabetes. Diabet Med. 2014;31(12):1542–9.
104. Ramachandran A, *et al*. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. Lancet Diabetes Endocrinol. 2013;1(3):191–8.
105. Ramachandran A, *et al*. Predictive value of HbA1c for incident diabetes among subjects with impaired glucose tolerance – analysis of the Indian Diabetes Prevention Programmes. Diabet Med. 2012;29(1):94–8.
106. Anjana RM, ICMR–INDIAB Collaborative Study Group, *et al*. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia. 2011;54(12):3022–7.
107. Ramachandran A, Indian Diabetes Prevention Programme (IDPP), *et al*. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289–97.
108. Ramachandran A, *et al*. Persistent impaired glucose tolerance has similar rate of risk factors as for diabetes – results of Indian diabetes prevention programme (IDPP). Diabetes Res Clin Pract. 2006;73(1):100–3.
109. Ramachandran A, *et al*. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). Diabetes Care. 2007;30(10): 2548–52.
110. Snehalatha C, *et al*. Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme. Diabetes Vasc Dis Res. 2008;5(1):25–9.
111. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016. doi: 10.1038/nrendo.2016.53. [Epub ahead of print]. Online ahead of print.

Source: Joshi S.R., Aravind S.R. (2017) Diabetes in India and Southeast Asia. In: Dagogo-Jack S. (eds) Diabetes Mellitus in Developing Countries and Underserved Communities. Springer, Cham. https://doi.org/10.1007/978-3-319-41559-8_6.

2

Continuous Glucose Monitoring and Glycemic Variability

J. Zhou, W. Jia

Continuous glucose monitoring (CGM) technology can comprehensively and accurately reflect the characteristics of glycemic variability. Currently, research on glycemic variability using CGM is one of the hot spots (Fig. 1). Previously, we have analyzed the glucose profiles of individuals with different glucose tolerances by reviewing retrospective CGM data, and here are some of our findings: (1) despite the influence of various factors, the fasting plasma glucose (FPG) usually fluctuates between 3.9 and 5.6 mmol/L by the regulation of the nervous and endocrine systems and the liver. The blood glucose levels begin to rise about 10 min after meal intake, due to the absorption of carbohydrates in the diet. The peak postprandial blood glucose level and duration time are associated with a variety of factors such as eating time and the amount and content of food intake. Usually, the blood glucose concentration peaks at 1 h after eating and returns to the premeal level after 2–3 h. The intraday and inter-day blood glucose excursions were reported to be approximately 2.0 mmol/L and 0.8 mmol/L [1]. (2) The intra-day glycemic variability of patients with impaired glucose tolerance was significantly increased by 50%, as compared with that of those with normal glucose tolerance. However, no significant difference in the inter-day glycemic variability was found [2, 3] (Fig. 2). (3) Once the patients were diagnosed as diabetes, the intra-day glycemic variability was further increased, accompanied by significantly increased inter-day variability, which are 3- and 2.5-fold increased, respectively, as compared to that in individuals with normal glucose tolerance. However, no significant difference was found in the frequency of intraday glycemic variability [3] (Figs. 3 and 4). (4) Due to a lack of early-phase insulin secretion, the postprandial glucose concentration excessively rises and lasts for a long time, with predominant hyperglycemia after breakfast [1]. (5) Glycated hemoglobin A_{1c} (HbA_{1c}) represents the overall level of blood glucose but does not reflect the characteristics of glycemic variability. The mean amplitude of glycemic excursion (MAGE) and mean of daily differences (MODD) obtained

J. Zhou, W. Jia (✉)
Department of Endocrinology and Metabolism, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
e-mail: wpjia@sjtu.edu.cn

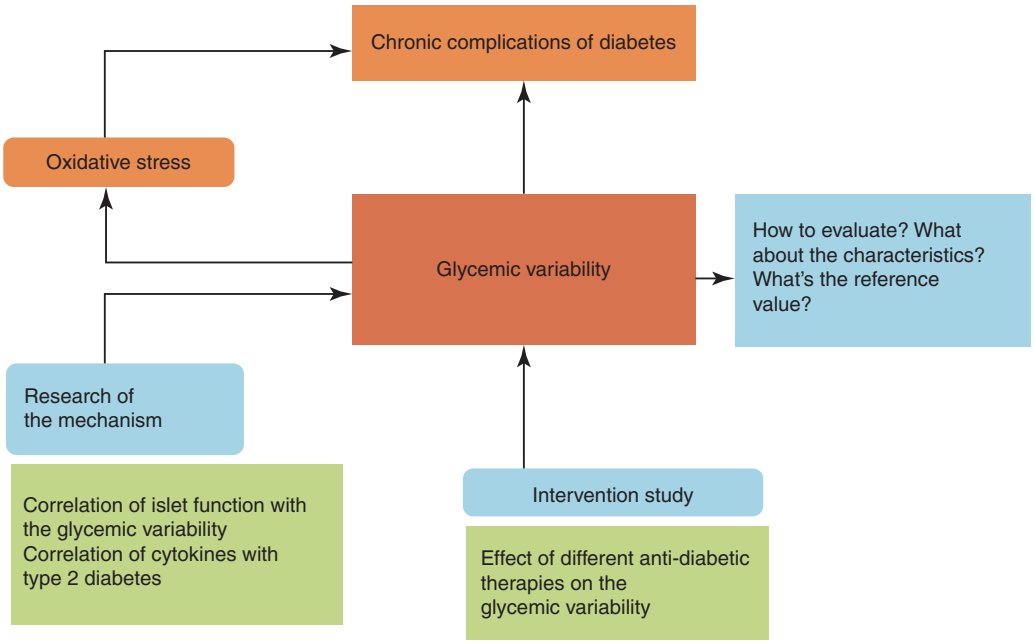


Fig. 1: The main content of CGM-based research on glycemic variability.

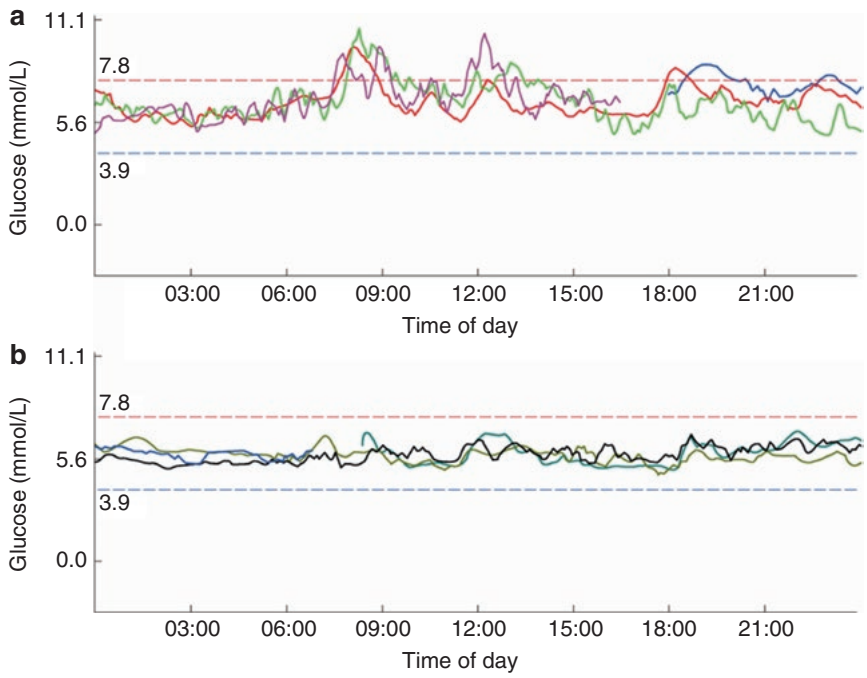


Fig. 2: The CGM profiles of one case of impaired glucose tolerance (**a**) and one case of normal glucose tolerance (**b**).

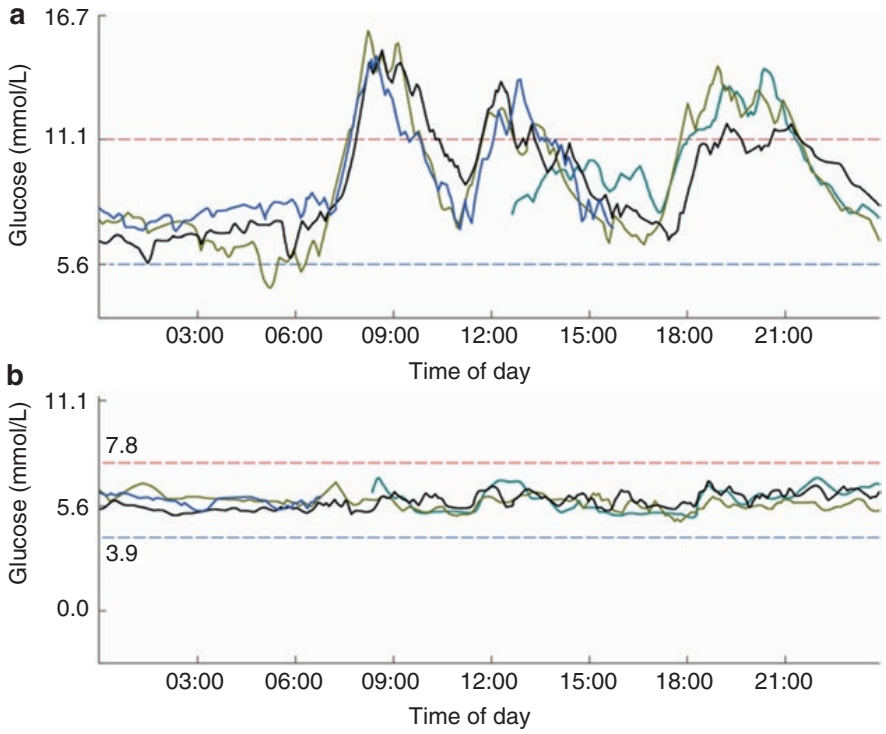


Fig. 3: The CGM profiles of one case of type 2 diabetes mellitus (**a**) and one case of normal glucose tolerance (**b**).

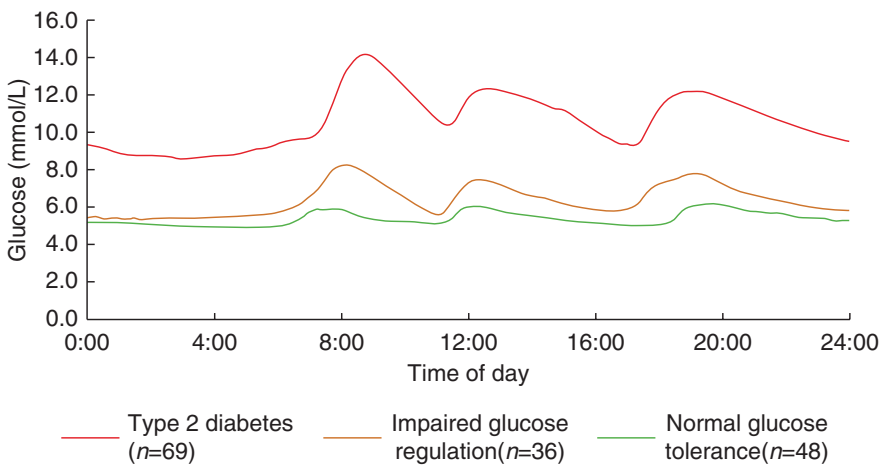


Fig. 4: The characteristics of glycemic variability in individuals with different state of glucose tolerance using CGM. Note: The blood glucose levels fluctuate with small amplitudes in healthy individuals. However, individuals with impaired glucose tolerance exhibited increased glycemic variability compared with normal individuals, and the overall glucose level and glycemic variability were significantly increased in type 2 diabetes patients.

in CGM glucose profiles can accurately reflect the magnitude of intraday and inter-day glycemic variability of subjects. Both parameters may serve as clinical parameters for assessing whether type 2 diabetes patients achieve the target glycemic control [2].

Relationship Between Glycemic Variability and Diabetic Microvascular Complications

With advances in CGM technology, further investigation is carried out to explore the relationship between glycemic variability and diabetic microvascular complications. Šoupal *et al.* [4] found that standard deviation of blood glucose (SDBG) calculated from CGM data was associated with diabetic microangiopathy in 32 type 1 diabetes patients. Similarly, Sartore *et al.* [5] reported a correlation between SDBG and the development of diabetic retinopathy by analyzing the CGM data from 68 type 1 or type 2 diabetes patients. We previously investigated the relationship between glycemic variability and microalbuminuria in 176 type 2 diabetes patients with an HbA_{1c} <6.5% (48 mmol/mol) and found that the glycemic variability was very different among these patients (Fig. 5). More than half of the patients presented abnormal glycemic variability, which were associated with increased risk of microalbuminuria (Fig. 6), indicating that glycemic variability is a risk factor of the occurrence of microalbuminuria in type 2 diabetes [6]. Nevertheless, the Diabetes

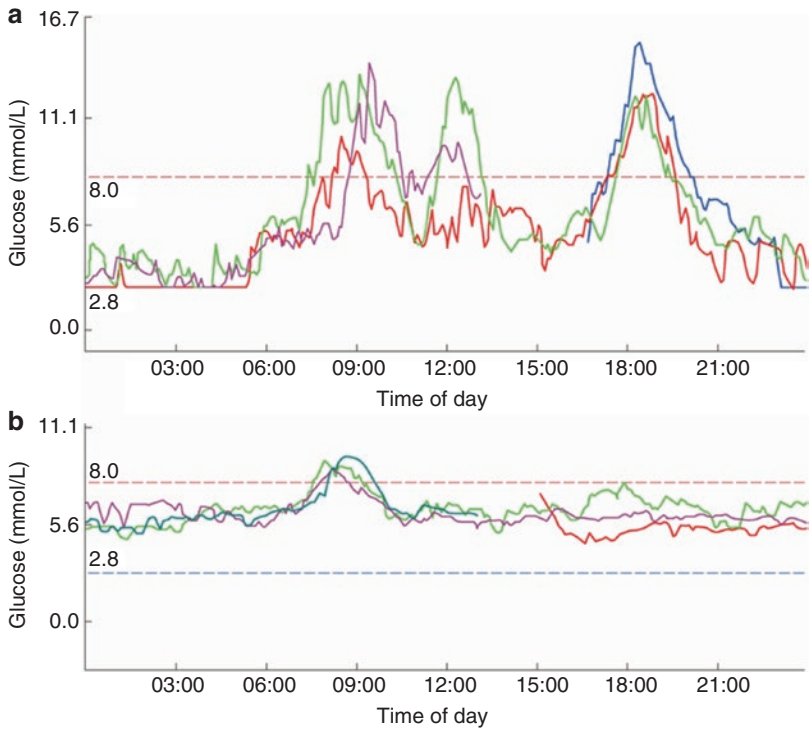


Fig. 5: The CGM profiles of two cases of type 2 diabetes with HbA_{1c} <6.5% (48 mmol/mol) [6]. Note: (**a**) HbA_{1c} 6.4% (46 mmol/mol), MAGE 3.0 mmol/L; (**b**) HbA_{1c} 6.2% (44 mmol/mol), MAGE 0.9 mmol/L.

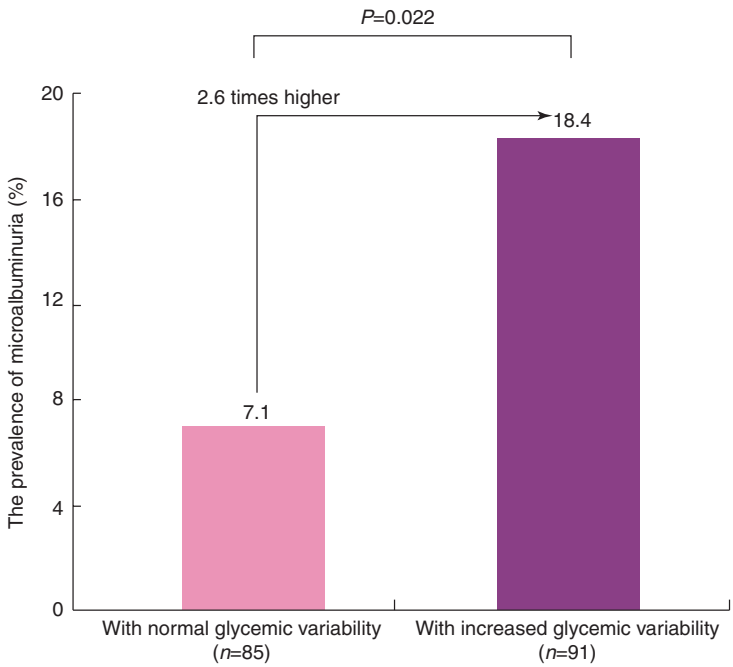


Fig. 6: The detection rate of microalbuminuria in type 2 diabetes with HbA_{1c} <6.5% (48 mmol/mol) who had normal or abnormal glycemic variability [6].

Control and Complications Trial (DCCT) results show that glycemic variability is not an independent risk factor for complications. Lachin *et al.* [7] published an article, demonstrating that only the M-value is correlated to microalbuminuria but not retinopathy. At present, however, the correlation between glycemic variability and diabetic microvascular complications still remains undetermined.

Relationship Between Glycemic Variability and Diabetic Macrovascular Complications

The relationship between glycemic variability and macrovascular complications has also been a hot research topic in recent years. In the study performed by Chen *et al.* [8], 36 type 2 diabetes patients were classified into two groups according to the levels of carotid intima-media thickness (IMT) as patients with or without atherosclerosis. Compared to controls, the MAGE level calculated from CGM data was gradually increased with the progression of atherosclerosis. Also, the carotid IMT was correlated with age, duration of diabetes, and MAGE by Spearman's correlation analysis. Another study showed that during the DCCT, MBG was a better predictor of the macrovascular complications of type 1 diabetes than HbA_{1c} [9]. These findings suggested that glycemic variability is an important factor contributing to the progression of atherosclerosis in type 2 diabetes patients.

Also, we conducted a cross-sectional study in 216 type 2 diabetes patients to investigate the relationship between glycemic variability and macrovascular complications [10]. Magnetic resonance angiography (MRA) was applied to detect the severity of arterial stenosis, and ultrasonography was used to quantify carotid IMT as an index of subclinical atherosclerosis. Subcutaneous interstitial glucose concentrations of patients were monitored continuously for 3 days using the CGM system. The results revealed that age, increased systolic blood pressure, and increased mean blood glucose (MBG), but not glycemic variability, were independently related to atherosclerotic stenosis. In patients without cervical and/or intracranial lesions evaluated by MRA, SDBG and MAGE were both significantly related to carotid IMT (Figs. 7 and 8), revealing the intriguing possibility that glycemic variability plays a key role in the subclinical stage of atherosclerosis. Su *et al.* [11] analyzed the contribution of MAGE, blood glucose, and HbA_{1c} to the major adverse cardiac events in 222 patients with acute myocardial infarction. CGM system was used for 48 consecutive

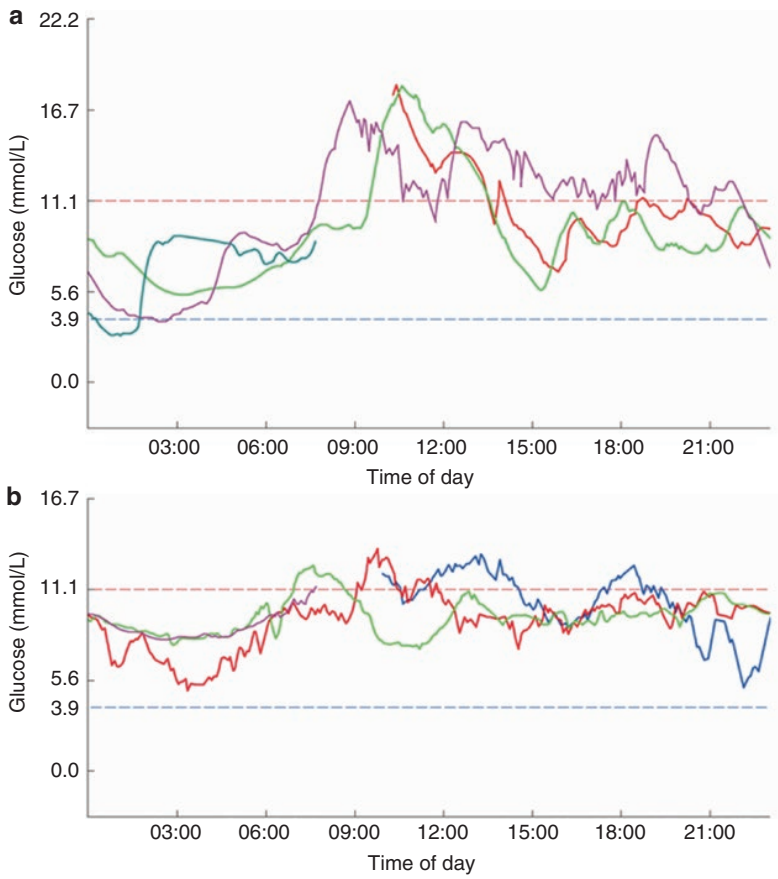


Fig. 7: Examples of the CGM profiles and carotid IMT measurements of two cases of type 2 diabetes patients with different glycemic variability. Note: (**a**) carotid IMT 1.0 mm, MAGE 7.99 mmol/L, SDBG 3.43 mmol/L; (b) carotid IMT: 0.6 mm, MAGE: 3.06 mmol/L, SDBG 1.42 mmol/L. *carotid IMT* carotid intima-media thickness, *MAGE* mean amplitude of glycemic excursion, *SDBG* standard deviations of blood glucose

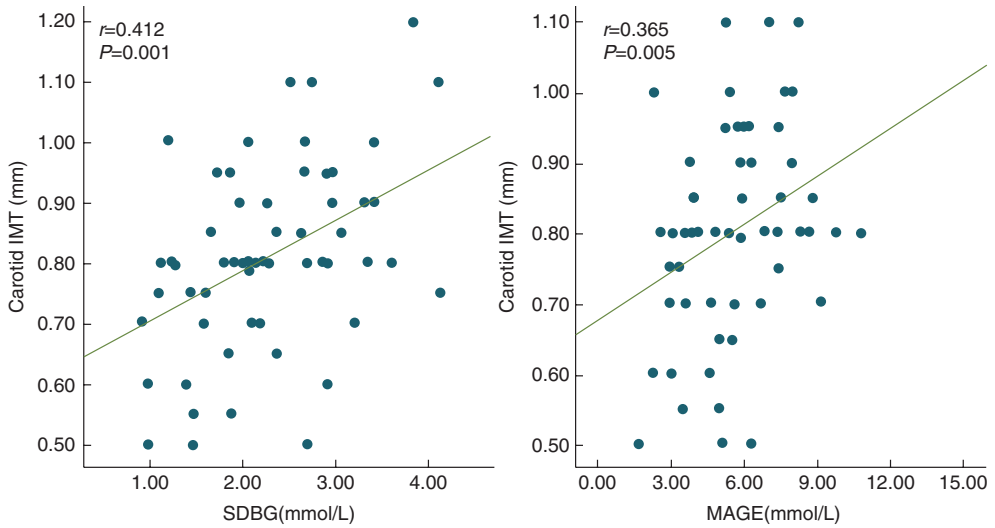


Fig. 8: The correlation between glycemic variability and carotid IMT in 63 type 2 diabetes patients without atherosclerotic stenosis as determined by cranial/cervical magnetic resonance angiography [10] (Reprint from *Cardiovascular Diabetology*). Note: *IMT* intima-media thickness, *SDBG* standard deviations of blood glucose, *MAGE* mean amplitude of glycemic excursion

hours after admission. Based on the cutoff reference value of MAGE as 3.9 mmol/L established by our previous study [12], patients were divided into two groups as high MAGE (≥3.9 mmol/L) or low MAGE (<3.9 mmol/L). The results demonstrated that MAGE was independently correlated with the incidence of major adverse cardiac events. Similar findings were obtained by Wang *et al.* [13]. In another study performed by Su *et al.* [14], coronary artery angiography was performed in 344 type 2 diabetes with chest pain, and the Gensini score was calculated to assess the severity of coronary artery disease. The results demonstrated that MAGE, calculated from CGM data, was the most distinct independent predictor of coronary artery disease. In addition, in a study of 22 type 1 diabetes patients, MAGE was independently correlated with the change in aortic diastolic pressure during hyperglycemic clamp, suggesting the involvement of daily glucose variability in the progression of macrovascular disease [15]. In 2006, Monnier *et al.* [16] found that urinary 8-iso prostaglandin $F_{2\alpha}$ excretion rates, an indicator of oxidative stress, were higher in type 2 diabetes patients than in healthy controls, and it was significantly correlated with MAGE ($r = 0.86$, $P < 0.001$). Thus, they concluded that MAGE is an important parameter reflecting glycemic variability [17], and glycemic variability is involved in macrovascular complications [18]. It is noted that Xu *et al.* [19] found a significant relationship between MAGE and cardiac autonomic neuropathy in newly diagnosed type 2 diabetes, which demonstrating that glycemic variability is an important risk factor for cardiovascular autonomic neuropathy. Therefore, persistent hyperglycemia (including basal hyperglycemia, postprandial hyperglycemia) and glycemic variability (postprandial hyperglycemia or hypoglycemia) are both involved in macrovascular complications development through different mechanisms (Fig. 9).

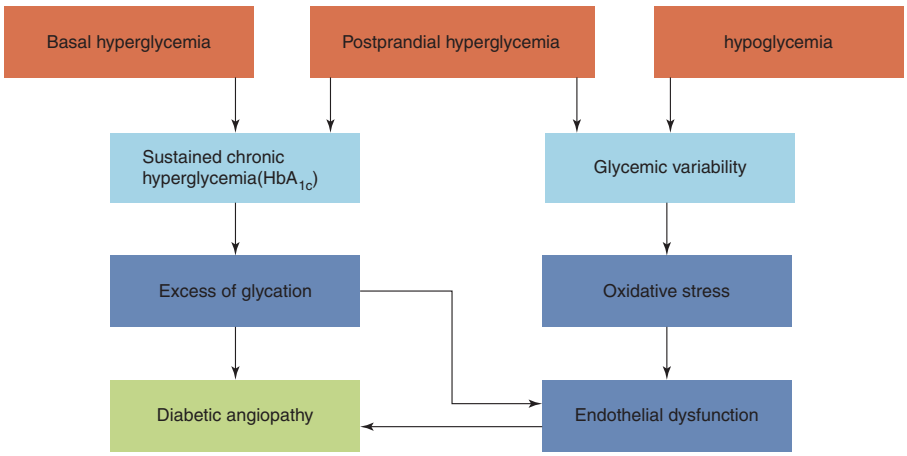


Fig. 9: Effect of persistent hyperglycemia (basal hyperglycemia, postprandial hyperglycemia) and glycemic variability (postprandial hyperglycemia and hypoglycemia) on chronic complications of diabetes mellitus.

Relationship Between Glycemic Variability and Islet Function

Currently, impaired insulin secretion and/or decreased insulin sensitivity are generally accepted as basic pathophysiological characteristics of diabetic patients. Islet β-cell function plays an important role in the progression of diabetes mellitus, and its dynamic changes in "quality" and "quantity" have crucial impact on the regulation of blood glucose and the occurrence of chronic complications. We previously analyzed the relationship between glycemic variability and pathophysiological state in 339 healthy subjects with normal glucose regulation [20]. The results showed that early-phase insulin secretion (expressed as $\Delta I_{30}/\Delta G_{30}$) was significantly different among healthy subjects with different MAGE values, whereas basal insulin secretion and insulin sensitivity were not significantly different (Fig. 10). The correlation analysis showed that glycemic variability was negatively correlated with early-phase insulin secretion (Fig. 11), indicating that excessive glycemic variability was associated with poor islet function. These data suggested that early changes in islet function could impact glycemic variability. Our previous CGM data from type 2 diabetes patients with HbA_{1c} <6.5% (48 mmol/mol) showed that glucose profiles could greatly differ even among those with HbA_{1c} controlled within the target range. In addition to the duration of diabetes, the postprandial 30-min serum C-peptide level was also an independent factor, which to a certain extent reflects early-phase insulin secretion in type 2 diabetes [6]. These findings were further proven by Kohnert *et al.* [21], who conducted a study including 59 type 2 diabetes patients (age 64.2 ± 8.6 years old; HbA_{1c} 6.5 ± 1.0% (48 ± 11 mmol/mol); body mass index [BMI] 29.8 ± 3.8 kg/m^2) using either oral hypoglycemic agents (n = 34) or diet control alone (n = 25). The glucose profiles obtained from CGM measurements recorded over 3 consecutive days were analyzed. Postprandial β-cell function and basal β-cell function were measured by an insulin secretion model during a mixed-meal test. The insulin sensitivity was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR). The results showed that MAGE was nonlinearly correlated with postprandial β-cell function (r = 0.54, P < 0.001) and with basal

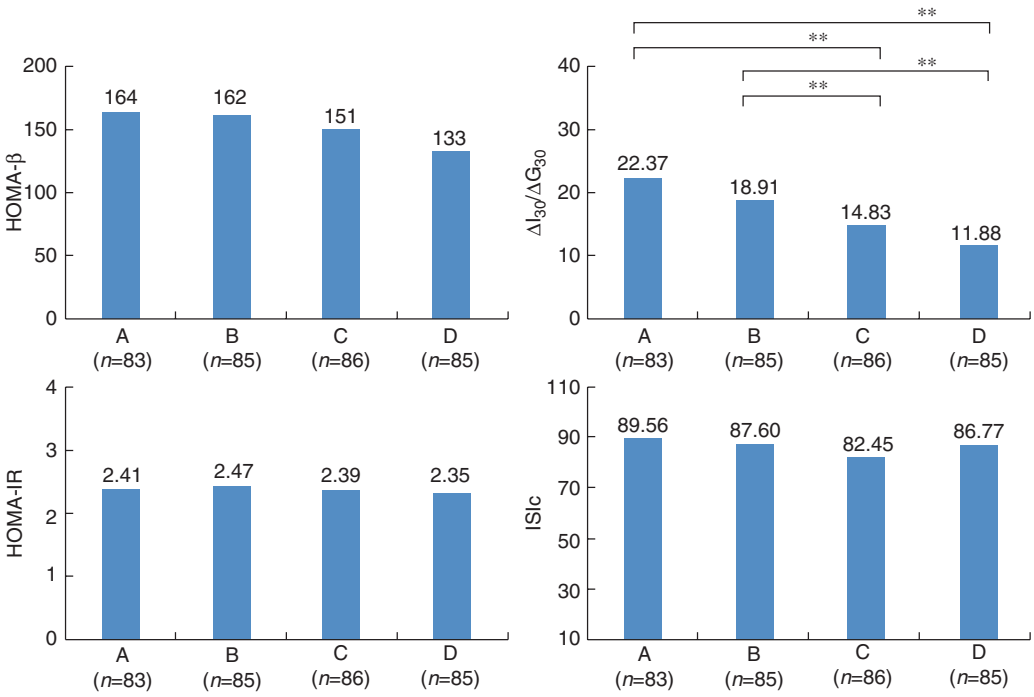


Fig. 10: Comparison of insulin secretion function and sensitivity in 339 patients with normal glucose tolerance but different MAGE levels [20] (Reprint with permission from *Chinese Journal of Diabetes Mellitus*) $^{**}P < 0.01$.

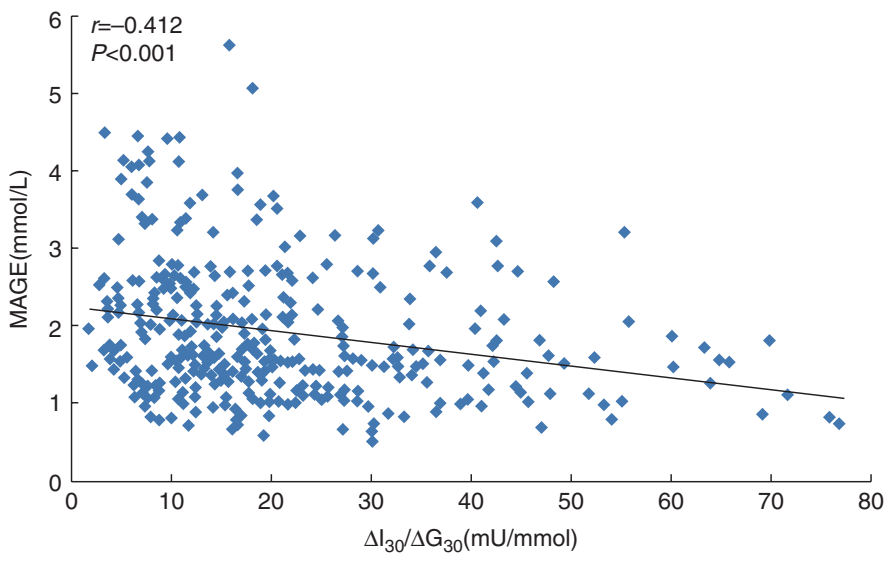


Fig. 11: The relationship between MAGE and islet function ($\Delta I_{30}/\Delta G_{30}$) in 339 individuals with normal glucose tolerance [20] (Reprint with permission from *Chinese Journal of Diabetes Mellitus*).

β-cell function ($r = 0.31$, $P = 0.025$) in oral hypoglycemic agent users but failed to correlate with these parameters in patients treated with diet modification alone. The stepwise multiple regression analysis demonstrated that postprandial β-cell function and treatment with oral hypoglycemic agents were independent contributors to MAGE ($R^2 = 0.50$, $P < 0.01$). This study demonstrated a close relationship between glycemic variability and postprandial β-cell function in type 2 diabetes patients using oral hypoglycemic agents. Therefore, we speculate that compared to other pathophysiological factors such as insulin sensitivity and basal insulin secretion, early-phase islet is more closely associated with glycemic variability. Moreover, improvement in postprandial β-cell function appears to be an important target to reduce glycemic variability, thereby preventing the development and progression of diabetes complications. In addition, we have investigated the relationship between glycemic variability and cytokines. The results showed that the serum osteocalcin concentration increases with a decrease in the glucose concentration, and high initial osteocalcin levels are associated with subsequent improvements in glycemic variability [22].

The above studies show that abnormal glycemic variability may be an important contributor to the development of diabetes-related complications. According to FLAT-SUGAR Trial, compared with basal-bolus insulin, glucagon-like peptide-1 receptor agonist and insulin (GLIPULIN) can reduce glycemic variability, weight, and some cardiometabolic risk markers while maintaining equivalent HbA_{1c} levels [23]. Islet β-cell function and certain cytokines (such as osteocalcin, etc.) can affect blood glucose levels. The data analysis from CGM can accurately and comprehensively reflect glycemic variability. Therefore, it is necessary to carry out further researches in the future, especially prospective, large-scale studies using CGM, to clarify the relationship between glycemic variability and diabetic complications as well as the underlying mechanism, and finally, to provide new strategies for the prevention and treatment of diabetes and complications.

Statement on Consent for Participation

All the clinical trials carried out by the authors in this book have been reported to the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital already and were in accordance with the Good Clinical Practice and Standards of China Association for Ethical Studies (approval number: 2007-45).

References

1. Zhou J, Jia W, Yu M, Ma X, Bao Y, Lu W. The features of postprandial glucose state in type 2 diabetes mellitus. Zhonghua Yi Xue Za Zhi. 2006;86:970–5. https://doi.org/10.3760/j:issn:0376-2491.2006.14.009
2. Zhou J, Yu M, Jia WP, Li Q, Li M, Ma XJ, Lu W, Xiang KS. Application of continuous glucose monitoring system in the assessment of within-day and day-to-day blood glucose excursions in type 2 diabetic patients. Chin J Endocrinol Metab. 2006;22:286–8. https://doi.org/10.3760/j:issn:1000-6699.2006.03.028
3. Zhou J, Jia WP, Yu M, Bao YQ, Ma XJ, Lu W, Hu C, Yu HY, Xiang KS. Characteristics of glycemic stability in subjects with different glucose tolerance: the results of continuous glucose monitoring. Shanghai Med J. 2008;31:10–3.
4. Šoupal J, Škrha J Jr, Fajmon M, Horová E, Mráz M, Škrha J, Prázný M. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. Diabetes Technol Ther. 2014;16:198–203. https://doi.org/10.1089/dia.2013.0205
5. Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. Acta Diabetol. 2013;50:437–42. https://doi.org/10.1007/s00592-013-0459-9

6. Zhou J, Jia W, Ma X, Bao YQ, Lu W, Li M, Li Q, Hu C, Xiang KS. Relationship between blood glucose variability and microalbuminuria in type 2 diabetic patients with well-controlled glycosylated hemoglobin. Zhonghua Yi Xue Za Zhi. 2008;88:2977–81. https://doi.org/10.3321/j:issn:0376-2491.2008.42.007
7. Lachin JM, Bebu I, Bergenstal RM, Pop-Busui R, Service FJ, Zinman B, Nathan DM, DCCT/EDIC Research Group. Association of glycemic variability in type 1 diabetes with progression of microvascular outcomes in the diabetes control and complications trial. Diabetes Care. 2017;40:777–83. https://doi.org/10.2337/dc16-2426
8. Chen XM, Zhang Y, Shen XP, Huang Q, Ma H, Huang YL, Zhang WQ, Wu HJ. Correlation between glucose fluctuations and carotid intima-media thickness in type 2 diabetes. Diabetes Res Clin Pract. 2010;90:95–9. https://doi.org/10.1016/j.diabres.2010.05.004
9. Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia. 2008;51:365–71. https://doi.org/10.1007/s00125-007-0883-x
10. Mo Y, Zhou J, Li M, Wang Y, Bao Y, Ma X, Li D, Lu W, Hu C, Li M, Jia W. Glycemic variability is associated with subclinical atherosclerosis in Chinese type 2 diabetic patients. Cardiovasc Diabetol. 2013;12:15. https://doi.org/10.1186/1475-2840-12-15
11. Su G, Mi SH, Tao H, Li Z, Yang HX, Zheng H, Zhou Y, Tian L. Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care. 2013;36:1026–32. https://doi.org/10.2337/dc12-0925
12. Zhou J, Li H, Ran X, Yang W, Li Q, Peng Y, Li Y, Gao X, Luan X, Wang W, Jia W. Establishment of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. Med Sci Monit. 2011;17:CR9–13. https://doi.org/10.12659/MSM.881318
13. Wang X, Zhao X, Dorje T, Yan H, Qian J, Ge J. Glycemic variability predicts cardiovascular complications in acute myocardial infarction patients with type 2 diabetes mellitus. Int J Cardiol. 2014;172:498–500. https://doi.org/10.1016/j.ijcard.2014.01.015
14. Su G, Mi S, Tao H, Li Z, Yang H, Zheng H, Zhou Y, Ma C. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovasc Diabetol. 2011;10:19. https://doi.org/10.1186/1475-2840-10-19
15. Gordin D, Rönnback M, Forsblom C, Mäkinen V, Saraheimo M, Groop PH. Glucose variability, blood pressure and arterial stiffness in type 1 diabetes. Diabetes Res Clin Pract. 2008;80:e4–7. https://doi.org/10.1016/j.diabres.2008.01.010
16. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295:1681–7. https://doi.org/10.1001/jama.295.14.1681
17. Monnier L, Colette C, Boegner C, Pham TC, Lapinski H, Boniface H. Continuous glucose monitoring in patients with type 2 diabetes: Why? When? Whom? Diabetes Metab. 2007;33:247–52. https://doi. org/10.1016/j.diabet.2006.11.007
18. Monnier L, Colette C, Owens D. The glycemic triumvirate and diabetic complications: is the whole greater than the sum of its component parts? Diabetes Res Clin Pract. 2012;95:303–11. https://doi.org/10.1016/j.diabres.2011.10.014
19. Xu W, Zhu Y, Yang X, Deng H, Yan J, Lin S, Yang H, Chen H, Weng J. Glycemic variability is an important risk factor for cardiovascular autonomic neuropathy in newly diagnosed type 2 diabetic patients. Int J Cardiol. 2016;215:263–8. https://doi.org/10.1016/j.ijcard.2016.04.078
20. Zhou J, Li H, Yang WY, Ran XW, Li Q, Peng YD, Li YB, Gao X, Luan XJ, Wang WQ, Jia W. Relationship between early-phase insulin secretion and blood glucose variability in subject with normal glucose regulation. Chin J Diabetes Mellitus. 2009;1:89–93. https://doi.org/10.3760/cma.j.issn.1674-5809.2009.02.004
21. Kohnert KD, Augstein P, Zander E, Heinke P, Peterson K, Freyse EJ, Hovorka R, Salzsieder E. Glycemic variability correlates strongly with postprandial beta-cell dysfunction in a segment of type 2 diabetic patients using oral hypoglycemic agents. Diabetes Care. 2009;32:1058–62. https://doi.org/10.2337/dc08-1956
22. Bao YQ, Zhou M, Zhou J, Lu W, Gao YC, Pan XP, Tang JL, Lu HJ, Jia WP. Relationship between serum osteocalcin and glycaemic variability in type 2 diabetes. Clin Exp Pharmacol Physiol. 2011;38:50–4. https://doi.org/10.1111/j.1440-1681.2010.05463.x
23. FLAT-SUGAR Trial Investigators. Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus glp-1 agonist in participants with type 2 diabetes at high cardiovascular risk. Diabetes Care. 2016;39:973–81. https://doi.org/10.2337/dc15-2782

Source: Zhou J., Jia W. (2018) Continuous Glucose Monitoring and Glycemic Variability. In: Jia W. (eds) Continuous Glucose Monitoring. Springer, Singapore. https://doi.org/10.1007/978-981-10-7074-7_11.

3

Diabetes and Frailty

Mitsutaka Yakabe, Sumito Ogawa

Abstract

Frailty is an age-related condition characterized by a decline in the reserve capacity of multiple physiological systems, which leads to geriatric syndromes, disability, and mortality. Frailty is often observed among diabetic patients. In the clinical practice for frail diabetic elderly, glycemic control should be personalized in order to minimize the risk of severe hypoglycemia and hyperglycemia. Other interventions for frailty with diabetes include nutrition, exercise, and avoiding polypharmacy.

Keywords Frailty, Fatigue, Falls, Geriatric syndrome

Introduction

Worldwide population aging is accelerating, and the most problematic expression of population aging is the clinical condition of frailty. Frailty develops as a consequence of age-related decline in multiple physiological systems, which results in a vulnerability to sudden health status changes triggered by relatively minor stressor events [1]. In this chapter, we describe the relationship between frailty and diabetes and the management of frailty with diabetes.

Definition of Frailty

Frailty is a dynamic, age-related condition characterized by a decline in the reserve capacity of multiple physiological systems [1]. When exposed to an apparently small stress, such as a new drug, minor illness, or minor surgery, a healthy elderly can almost entirely recover in a relatively short time. In a frail elderly, however, resistance to stressors is decreased. Therefore, the stress results in a striking and disproportionate change in health state—i.e., from independent to

M. Yakabe, S. Ogawa (✉)
Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1, Bunkyo-ku, Tokyo, Japan
e-mail: suogawa-tky@umin.ac.jp

dependent, mobile to immobile, postural stability to proneness to falling, or lucid to delirious—and the person's functional ability might not recover to the previous level even after the stress was removed.

Frailty is supposed to be one of geriatric syndromes. It leads to increased risk of adverse health outcomes, such as low mobility, falls, functional decline, hospitalization, and death. The world is aging rapidly, and the number of frail elderly will lead to increased cost of healthcare and social security [2].

Clinical Presentations of Frailty

Fatigue

In older adults, fatigue is common and associated with functional deficits and survival. A simple question whether the patient "feels tired most of the time" could identify older adults with a higher risk of mortality [3].

Falls

Balance and gait impairment are major features of frailty and are important risk factors for falls. Spontaneous falls occur in severe frailty and are typically repeated, associated with fear of further falls that makes the patient less mobile [1].

Delirium

Delirium is characterized by the rapid onset of fluctuating confusion and impaired awareness. Delirium is related to reduced integrity of brain function and is independently associated with adverse outcomes [1].

Others

Frail elderly are susceptible to unintended weight loss, frequent infections, and fluctuating disability [1].

Pathophysiology of Frailty

Many organ systems have redundant capacity. A gradual decrease in physiological reserve occurs with aging. However, this decrease is accelerated in frailty and homeostatic mechanisms start to fail. Aging promotes cumulative decline in several physiological systems, the subsequent depletion of homeostatic reserve, and vulnerability to disproportionate changes in health status after minor stressor events. These complex aging mechanisms are determined by underlying genetic, epigenetic, and environmental factors [1].

In a cross-sectional study of 1002 women, abnormality in three or more systems among six different physiological systems (hematological, inflammatory, hormonal, adiposity, neuromuscular, and micronutrient) was a strong predictor of frailty. The brain, endocrine system, immune system, and skeletal muscle are intrinsically interrelated and are the organ systems that are best studied in the development of frailty [1].

The Frail Brain

Aging is associated with structural and physiological changes in the brain. In particular, the hippocampus could be affected by changes in synaptic function, protein transport, and mitochondrial function, which is involved in the pathophysiology of cognitive decline and Alzheimer's dementia. The aging brain is also characterized by structural and functional changes to microglial cells, which are activated by brain injury and local and systemic inflammation and become primed to small stimuli with aging, potentially causing damage and neuronal death [1].

The Frail Endocrine System

The brain and endocrine system are linked intrinsically through the hypothalamo-pituitary axis, which controls metabolism and energy use through the signaling action of hormones. During aging, production of three major circulating hormones decreases—(1) insulin-like growth factor-1 (IGF-1) and growth hormone, (2) sex hormones (estrogen and estradiol), and (3) adrenocortical hormones [1]. These could also be involved in the development of frailty.

The Frail Immune System

The aging immune system is characterized by a reduction in stem cells, changes in T-lymphocyte production, blunting of the B-cell-controlled antibody response, and reduced phagocytic activity of neutrophils, macrophages, and natural killer cells. This senescent immune system might function adequately in the quiescent state but might fail to respond appropriately to the stress of acute inflammation. Evidence suggests that chronic low-grade inflammation has a major role in the pathophysiology of frailty. Several inflammatory cytokines have been associated with frailty: interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNFα), and C-X-C motif chemokine ligand-10 (CXCL10) [1].

The Frail Skeletal Muscle (Sarcopenia)

Sarcopenia is a debilitating condition characterized by progressive loss of muscle mass, strength, and function. It is common in elderly and results in frailty, disability, and high mortality [4]. Sarcopenia is supposed to be an aspect of physical frailty. Fried *et al*. proposed the cycle of frailty, in which sarcopenia was one of the main potential causes of frailty [5]. In this cycle, sarcopenia and five components of frailty—weight loss, exhaustion, weakness, slowness, and low physical activity—are closely related and create a vicious circle (Fig. 1) [6].

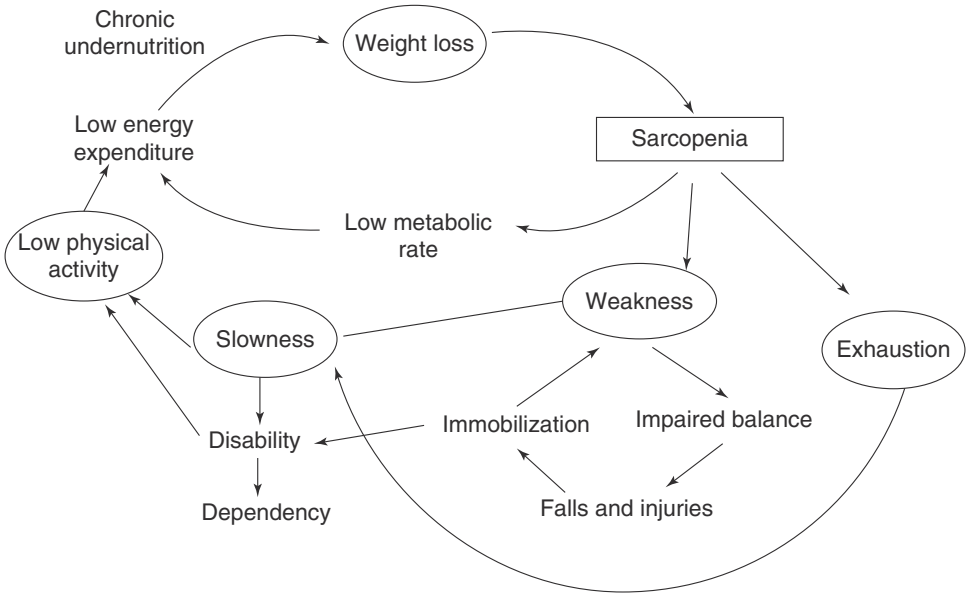


Fig. 1: The cycle of frailty (Adapted from Xue GL *et al.* [6]).

Diagnostic Criteria of Frailty

Frailty is considered potentially reversible. Therefore, early detection of frailty and proper interventions are important. However, its assessment still lacks gold standard. Instruments for assessing frailty can be divided into two categories: the physical phenotype models and the multi-domain models.

An example of the physical phenotype models commonly used is Fried's criteria [5]. Fried *et al.* determined frailty by five physical components: (1) unintentional weight loss, (2) exhaustion, (3) weakness, (4) slowness, and (5) low physical activity. Persons are diagnosed as pre-frail when one or two of the five components are present, and they are diagnosed as frail when three or more are present. Based on Fried's criteria, the Women's Health and Aging Studies (WHAS) and Cardiovascular Health Study (CHS) also present frailty-defining criteria [7] (Table 1).

The multi-domain models are based on a broader concept of frailty and include the decline in the medical, psychological, cognitive, functional, and social domains. One of the tools is the Kihon Checklist (KCL), which was established in Japan (Table 2) [8]. This score closely correlated with validated assessments of physical functions, nutritional state, cognitive function, depressive mood, and the number of frailty phenotypes defined by the CHS criteria. At a cutoff KCL score of 7/8, the sensitivity and specificity for estimating frailty were 89.5% and 80.7%, respectively. At a cutoff of 3/4 for pre-frail status, those for estimating pre-frail status were 70.3% and 78.3%, respectively.

Table 1: Proposed diagnostic criteria of frailty.

Components	Fried's criteria	CHS	WHAS
Weight loss	Unintentional loss of ≥4.5 kg in the past year	Baseline: Lost >10 pounds unintentionally in last year Follow-up: (weight in previous year-current weight)/(weight in previous year) ≥0.05 and the loss was unintentional	Baseline: Either of: 1. (weight at age 60—weight at exam)/(weight at age 60) ≥0.1 2. BMI at exam <18.5 Follow-up: Either of: 1. BMI at exam <18.5 2. (weight in previous year-current weight)/(weight in previous year) ≥0.05 and the loss was unintentional
Exhaustion	Poor endurance and energy, self-reported from the Center for Epidemiologic Studies Depression Scale	Self-report of either of: 1. Felt that everything I did was an effort in the last week 2. Could not get going in the last week	Self-report of any of: 1. Low usual energy level1 (≤3, range 0–10) 2. Felt unusually tired in last 2 months 3. Felt unusually weak in the past 2 months
Low physical activity	Lowest quintile of kilocalories of physical activity during the past week, measured by the Minnesota Leisure Activity Scale	Women: Kcal <270 on activity scale (18 items) Men: Kcal <383 on activity scale (18 items)	Women: Kcal <90 on activity scale (6 items) Men: Kcal <128 on activity scale (6 items)
Slowness	Walking speed under the lowest quintile adjusted for sex and height	Walking 15 feet (4.57 m) at usual pace Women: Time ≥7 s for height ≤159 cm Time ≥6 s for height >159 cm Men: Time ≥7 s for height ≤173 cm Time ≥6 s for height >173 cm	Walking 4 m at usual pace Women: Speed ≤4.57/7 m/s for height ≤159 cm Speed ≤4.57/6 m/s for height >159 cm Men: Speed ≤4.57/7 m/s for height ≤173 cm Speed ≤4.57/6 m/s for height >173 cm
Weakness	Handgrip strength in the lowest 20% quintile adjusted for sex and body mass index	Grip strength Women: ≤17 kg for BMI ≤23 ≤17.3 kg for BMI 23.1–26 ≤ 18 kg for BMI 26.1–29 ≤21 kg for BMI >29 Men: ≤29 kg for BMI ≤24 ≤30 kg for BMI 24.1–26 ≤30 kg for BMI 26.1–	Grip strength: Same as in CHS

Adapted from Fried *et al.* [5] and Xue QL *et al*. [7]

Table 2: The Kihon checklist [8].

Question		Score
1.	Do you go out by bus or train by yourself?	☐0. YES ☐1. NO
2.	Do you go shopping to buy daily necessities by yourself?	☐0. YES ☐1. NO
3.	Do you manage your own deposits and savings at the bank?	☐0. YES ☐1. NO
4.	Do you sometimes visit your friends?	☐0. YES ☐1. NO
5.	Do you turn to your family or friends for advice?	☐0. YES ☐1. NO
6.	Do you normally climb stairs without using handrail or wall for support?	☐0. YES ☐1. NO
7.	Do you normally stand up from a chair without any aids?	☐0. YES ☐1. NO
8.	Do you normally walk continuously for 15 min?	☐0. YES ☐1. NO
9.	Have you experienced a fall in the past year?	☐1. YES ☐0. NO
10.	Do you have a fear of falling while walking?	☐1. YES ☐0. NO
11.	Have you lost 2 kg or more in the past 6 months?	☐1. YES ☐0. NO
12.	Height, cm; weight, kg. If BMI (body mass index) is less than 18.5, this item is scored	☐1. YES ☐0. NO
13.	Do you have any difficulties eating tough foods compared to 6 months ago?	☐1. YES ☐0. NO
14.	Have you choked on your tea or soup recently?	☐1. YES ☐0. NO
15.	Do you often experience having a dry mouth?	☐1. YES ☐0. NO
16.	Do you go out at least once a week?	☐0. YES ☐1. NO
17.	Do you go out less frequently compared to last year?	☐1. YES ☐0. NO
18.	Do your family or your friends point out your memory loss? e.g., "You ask the same question over and over again"	☐1. YES ☐0. NO
19.	Do you make a call by looking up phone numbers?	☐0. YES ☐1. NO
20.	Do you find yourself not knowing today's date?	☐1. YES ☐0. NO
21.	In the last 2 weeks, have you felt a lack of fulfillment in your daily life?	☐1. YES ☐0. NO
22.	In the last 2 weeks, have you felt a lack of joy when doing the things you used to enjoy?	☐1. YES ☐0. NO
23.	In the last 2 weeks, have you felt difficulty in doing what you could do easily before?	☐1. YES ☐0. NO
24.	In the last 2 weeks, have you felt helpless?	☐1. YES ☐0. NO
25.	In the last 2 weeks, have you felt tired without a reason?	☐1. YES ☐0. NO
		Total score /25

The Relationship Between Type 2 Diabetes and Frailty

Diabetes has been associated with an increased risk of developing physical disability in elderly. Several studies have shown that diabetic patients aged 65 or over were more likely to be frail than nondiabetic elderly. These studies also reported that frail patients with diabetes had a higher mortality than non-frail patients, and the presence of frailty was an independent risk factor for mortality [9]. Diabetes mellitus is an independent fall risk factor among elderly nursing home residents [10]. Chronic conditions such as visual disturbances, diabetic complications, comorbidities, and depression could affect patients with diabetes and contribute to frailty.

One study shows that frailty was associated with increased risk of incident type 2 diabetes in community-dwelling nondiabetic elderly [11]. Frail elderly are supposed to have higher oxidative stress, higher levels of proinflammatory cytokines, increased deoxyribonucleic acid damage, and shorter telomere length. These might play a role in the pathogenesis of type 2 diabetes.

Psychological states such as depression are important aspects of frailty. One study reports that diabetic old men have a higher risk of depression than nondiabetic men and, interestingly, that the association of diabetes duration and the risk of depression is "J-shaped" [12].

One mechanism that diabetes causes frailty might be that it exacerbates inflammation. In a systematic review and meta-analysis of the relationship between inflammation and frailty, both frail and pre-frail elderly had significantly higher serum level of interleukin-6 and C-reactive protein (CRP) compared with non-frail elderly. Frailty and pre-frailty were also associated with elevated white blood cell and fibrinogen levels [13]. Another mechanism might be that sarcopenia and frailty may share the similar pathway for multiple pathologic processes in elderly. Sarcopenia may be an intermediate step in the development of frailty in patients with diabetes.

Management of Frailty with Type 2 Diabetes

The Goal of Glycemic Control

There is no definite guideline for type 2 diabetes in frail elderly. Very tight glucose control may often be not desirable. An HbA_{1c} less than 7% can increase the likelihood of hypoglycemia [14]. Fall risk markedly increased when HbA_{1c} was 7% or below, regardless of frailty status [15].

In 2012, the American Diabetes Association (ADA) and the American Geriatrics Society (AGS) recommended a team approach to treat older patients with diabetes, including individualized treatment plans and education to patients and their caregivers. The goal of treatment is to establish acceptable glycemic control and minimize the risk of acute complications such as hypoglycemia and serious hyperglycemia [16]. Blood pressure and lipid control are also described. They are shown in Table 3.

According to the International Diabetes Federation, an HbA_{1c} target of 7.0–8.0% is suitable for functionally independent older people with a reasonable life expectancy, and a target of ≤8.5% is appropriate for frail older people and those with dementia and a life expectancy of less than 10 years [17].

Table 3: A framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes [16].

Patient characteristics/health status	Rationale	Reasonable A_{1c} goal (a lower goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden)	Fasting or preprandial glucose (mg/dL)	Bedtime glucose (mg/dL)	Blood pressure (mmHg)	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive, and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/80	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild to moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150	100–180	<140/80	Statin unless contraindicated or not tolerated
Very complex/poor health (long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%	100–180	110–200	<150/90	Consider likelihood of benefit with statin (secondary prevention more so than primary)

Table 4: The guideline by the Japan Diabetes Society and the Japan Geriatrics Society for glycemic control in diabetes of the elderly.

Physical and cognitive status of patients		<Category 1> Normal cognitive function and normal ADL	<Category 2> "Mild cognitive impairment to mild dementia" or "lower IADL but normal BADL"	<Category 3> "Moderate to severe dementia" or "lower BADL" or "many comorbidities or multiple organ dysfunction"
Medication* with high risk of causing hypoglycemia used?	No	<7.0%	<7.0%	<8.0%
	Yes	6.5–7.4% (65–74 y.o.) 7.0–7.9% (over 75 y.o.)	7.0–7.9%	7.5–8.4%

*Insulin, sulfonylurea, or glinide

The DCPNS/PATH guidelines recommend that HbA_{1c} should be maintained at or above 8% rather than below a specific level because lower HbA_{1c} levels are associated with increased hypoglycemic events without accruing meaningful benefit for frail elderly [18]. The Italian Association of Medical Diabetologists has developed a guideline, in which six algorithms are proposed, and HbA_{1c} <9.0% is recommended for elderly frail patients with mild/moderate hyperglycemia [19].

In 2016, the Japan Diabetes Society and the Japan Geriatrics Society announced a guideline for glycemic control in diabetes of the elderly (Table 4). Characteristics of the guideline are that it sets goals depending on the patients' physical and cognitive status. They say that the goals could be set flexibly.

These guidelines might be useful, but setting personalized goals independent of these guidelines could be acceptable.

Medications

Elderly tend to have many morbidities and take many medicines. Polypharmacy is supposed to be a major cause of frailty in older persons. Prescriptions for frail elderly should be minimal. STOPP and START (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions and Screening Tool to Alert Doctors to the Right Treatment) are screening tools that identify potentially inappropriate prescribing in older adults [20]. For example, anticholinergic medicines can cause cognitive decline and frailty. Overtreatment of blood pressure results in hypotension and falls. Clinicians who prescribe elderly patients should understand the effect of aging on physiology and pharmacokinetics, balance risks versus benefits, and listen to patient and caregiver concerns.

Treatment based on DPP-4 (dipeptidyl peptidase-4) inhibitors might be beneficial for frail elderly [21]. They ensure high rates of adequate glycemic control, are associated with a low risk of hypoglycemia, appear to have a neutral effect on body weight, and can potentially improve quality of life.

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been developed and used in the treatment of type 2 diabetes. Effects of SGLT2 inhibitors on elderly people have not been well studied. According to a study about efficacy and safety of canagliflozin in individuals aged 75 or over, beneficial effects were observed, but overall incidence of adverse effects was higher in participants aged 75 or over than in those younger than 75 [22]. SGLT2 inhibitors could be a cause of weight loss. It should be recognized that frailty might not be a desirable indication for SGLT2 inhibitors.

One study shows that statin treatment was significantly associated with reduced 3-year mortality independently of age and multidimensional impairment in community-dwelling frail older patients with DM [23].

Nutrition and Weight Control

In general, diabetic patients should perform calorie restriction and control their weight in an appropriate range (e.g., BMI 18.5–25.0). However, this might not necessarily be applicable to frail elderly patients. Many older people do not consume sufficient amounts of dietary intake and protein. The current recommended dietary allowance (RDA) of dietary protein is 0.8 g/kg/day, but higher amount of protein might be needed for frail elderly. Caloric supplements between meals could increase weight and improve nutritional status. A review of guidelines recommends that elderly diabetic patients may have regular diets instead of diabetic diets, especially if they are in nursing homes [24].

Unintended weight loss and appetite loss are not rare in the elderly. Weight loss has been shown to be associated with accelerated mortality in older persons. It also leads to loss of muscle and bone, increasing frailty, falls, and hip fractures. When weight loss is observed in a frail elderly patient, there are various possible reasons, for example, internal diseases (such as cancers and infections), mental disorders (such as depression), medications, dysphagia, dental problems, eating problems, and social problems. Treatable causes of weight loss should not be overlooked.

Exercise

Resistance exercise involves muscles working hard against an applied force or weight such as in weight lifting. Aerobic exercise improves cardiovascular fitness and endurance capacity. Both exercises have been shown to prevent the decline in muscle mass and strength with age [9]. One resistance exercise training session per week could improve muscle strength.

Sarcopenia

Morley *et al.* suggested that the management of frailty in patients with diabetes initially should focus on the prevention of sarcopenia [25]. Until now, no pharmacologic agent has been proven to be as efficacious as nutrition plus exercise in order to prevent or treat sarcopenia, so this approach is the key strategy.

Treatable Causes of Fatigue

Treatable causes of fatigue should be considered: they include vitamin B12 deficiency, hypoadrenalism, hypothyroidism, anemia, sleep apnea, hypotension, syncope, and depression. Treatment of sleep apnea in diabetic individuals results in lower blood pressure, better glycemic control, and an improvement in quality adjusted life years. Depression is more common in diabetic individuals, and psychological and pharmacological interventions positively affect depression and improve glycemic control. Diabetes is commonly associated with autonomic neuropathy, which leads to orthostatic hypotension, arrhythmias, and syncope.

Type 1 Diabetes and Frailty

Few studies have described the management of frailty with type 1 diabetes. Older adults with type 1 diabetes are a heterogeneous group. With long-duration diabetes, hypoglycemia is common, regardless of HbA_{1c} level [26]. Individualized treatment plans using more complex insulin regimens and lower glycemic goals with frequent SMBG are recommended in healthy older adults. For frail elderly, however, it may be difficult to follow complex insulin regimens due to problems with cognition, mobility, vision, hearing, and depression. Guidelines for older individuals with type 1 diabetes are lacking, so the treatment could be based on the principles by the ADA and AGS [16]. The treatment regimens should be modified with the goal of minimizing hypoglycemia and severe hyperglycemia and maximizing quality of life [26].

Conclusions

Frailty is a serious problem in the era of world population aging. Especially in diabetic patients who are inclined to have comorbidities, early identification of frailty and proper interventions for frailty are important. Clinicians who examine diabetic elderly patients should be attentive to frailty and its complications, and personalized approach should be performed. Many clinical questions about frailty and diabetes remain unsolved. Further research is needed and more evidence should be established.

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62. doi:10.1016/s0140-6736(12)62167-9.
2. Azzopardi RV, Vermeiren S, Gorus E, Habbig AK, Petrovic M, Van Den Noortgate N, *et al*. Linking frailty instruments to the international classification of functioning, disability, and health: a systematic review. J Am Med Dir Assoc. 2016;17(11):1066.e1–1066.e11. doi:10.1016/j.jamda.2016.07.023.
3. Hardy SE, Studenski SA. Fatigue predicts mortality in older adults. J Am Geriatr Soc. 2008;56(10):1910–4. doi:10.1111/j.1532-5415.2008.01957.x.
4. Yakabe M, Ogawa S, Akishita M. Clinical Manifestations and Pathophysiology of Sarcopenia. Biomedical Sciences. 2015;1(2):10–7. doi:10.11648/j.rnat.20150102.11.
5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, *et al*. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.

6. Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci. 2008;63(9):984–90.
7. Xue QL. The frailty syndrome: definition and natural history. Clin Geriatr Med. 2011;27(1):1–15. doi:10.1016/j.cger.2010.08.009.
8. Satake S, Senda K, Hong YJ, Miura H, Endo H, Sakurai T, *et al*. Validity of the Kihon Checklist for assessing frailty status. Geriatr Gerontol Int. 2016;16(6):709–15. doi:10.1111/ggi.12543.
9. Jang HC. Sarcopenia, frailty, and diabetes in older adults. Diabetes Metab J. 2016;40(3):182–9. doi:10.4093/dmj.2016.40.3.182.
10. Maurer MS, Burcham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. J Gerontol A Biol Sci Med Sci. 2005;60(9):1157–62.
11. Veronese N, Stubbs B, Fontana L, Trevisan C, Bolzetta F, De Rui M, *et al*. Frailty is associated with an increased risk of incident type 2 diabetes in the elderly. J Am Med Dir Assoc. 2016;17(10):902–7. doi:10.1016/j.jamda.2016.04.021.
12. Almeida OP, McCaul K, Hankey GJ, Yeap BB, Golledge J, Norman PE, *et al*. Duration of diabetes and its association with depression in later life: The Health In Men Study (HIMS). Maturitas. 2016;86:3–9. doi:10.1016/j.maturitas.2016.01.003.
13. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, *et al*. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8. doi:10.1016/j.arr.2016.08.006.
14. Sinclair A, Morley JE. How to manage diabetes mellitus in older persons in the 21st century: applying these principles to long term diabetes care. J Am Med Dir Assoc. 2013;14(11):777–80. doi:10.1016/j.jamda.2013.09.001.
15. Nelson JM, Dufraux K, Cook PF. The relationship between glycemic control and falls in older adults. J Am Geriatr Soc. 2007;55(12):2041–4. doi:10.1111/j.1532-5415.2007.01430.x.
16. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, *et al*. Diabetes in older adults: a consensus report. J Am Geriatr Soc. 2012;60(12):2342–56. doi:10.1111/jgs.12035.
17. Sinclair A, Dunning T, Rodriguez-Manas L. Diabetes in older people: new insights and remaining challenges. Lancet Diabetes Endocrinol. 2015;3(4):275–85. doi:10.1016/s2213-8587(14)70176-7.
18. Mallery LH, Ransom T, Steeves B, Cook B, Dunbar P, Moorhouse P. Evidence-informed guidelines for treating frail older adults with type 2 diabetes: from the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) program. J Am Med Dir Assoc. 2013;14(11):801–8. doi:10.1016/j.jamda.2013.08.002.
19. Ceriello A, Gallo M, Candido R, De Micheli A, Esposito K, Gentile S, *et al*. Personalized therapy algorithms for type 2 diabetes: a phenotype-based approach. Pharmacogenomics Pers Med. 2014;7:129–36. doi:10.2147/pgpm.s50288.
20. Hill-Taylor B, Walsh KA, Stewart S, Hayden J, Byrne S, Sketris IS. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/ Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. J Clin Pharm Ther. 2016;41(2):158–69. doi:10.1111/jcpt.12372.
21. Avogaro A, Dardano A, de Kreutzenberg SV, Del Prato S. Dipeptidyl peptidase-4 inhibitors can minimize the hypoglycaemic burden and enhance safety in elderly people with diabetes. Diabetes Obes Metab. 2015;17(2):107–15. doi:10.1111/dom.12319.
22. Sinclair AJ, Bode B, Harris S, Vijapurkar U, Shaw W, Desai M, *et al*. Efficacy and safety of canagliflozin in individuals aged 75 and older with type 2 diabetes mellitus: a pooled analysis. J Am Geriatr Soc. 2016;64(3):543–52. doi:10.1111/jgs.14028.
23. Pilotto A, Panza F, Copetti M, Simonato M, Sancarlo D, Gallina P, *et al*. Statin treatment and mortality in community-dwelling frail older patients with diabetes mellitus: a retrospective observational study. PLoS One. 2015;10(6):e0130946. doi:10.1371/journal.pone.0130946.
24. CADTH Rapid Response Reports. Diabetic diets for frail elderly long-term care residents with type II diabetes mellitus: a review of guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health Copyright (c) 2015 Canadian Agency for Drugs and Technologies in Health; 2015.
25. Morley JE, Malmstrom TK, Rodriguez-Manas L, Sinclair AJ. Frailty, sarcopenia and diabetes. J Am Med Dir Assoc. 2014;15(12):853–9. doi:10.1016/j.jamda.2014.10.001.
26. Dhaliwal R, Weinstock RS. Management of type 1 diabetes in older adults. Diabetes Spectr. 2014;27(1):9–20. doi:10.2337/diaspect.27.1.9.

Source: Yakabe M., Ogawa S. (2018) Diabetes and Frailty. In: Yamagishi S. (eds) Diabetes and Aging-related Complications. Springer, Singapore. https://doi.org/10.1007/978-981-10-4376-5_12.

4

Insulin Injection and Blood Glucose Meter Systems

Julia Morera

Insulin Injections

Insulin Injection Devices

Vials and Syringes

The first disposable glass syringe was introduced in 1954 and was quickly replaced by a plastic syringe. Since then, disposable syringes from several manufacturers have been in widespread use and there are three different sizes with a lineage easy to trace: 0.3 ml (30 U), 0.5 ml (50 U) and 1 ml (100 U) with dose increments of 0.5 or 1 U, 1 U and 2 U, respectively.

These syringes are available with 6 mm, 8 mm and 12.7 mm needles.

The syringe is a historical device which has gradually been supplanted by insulin pens, except in the U.S.A., where syringes are still used by approximately 40% of patients taking insulin [1]. The decrease in syringe usage is mainly due to the inconvenience of carrying several materials and preparing the syringe for patients, the adverse psychological and social impacts of using a syringe, and failure to administer accurate doses (Table 1).

For cases of needle phobia, there is a specific device, Autoject® 2, in which an insulin syringe is integrated, allowing the user to hide the needle and automatically insert the needle and the contents of the syringe into the skin. This can be helpful in people suffering from a fear of needles.

Insulin Pens

Since the insulin pen was first manufactured in 1985, many improvements have been made to devices, leading to current pens with shorter and thinner needles, reduced injection force, color-coded insulin cartridges and packaging, and a built-it memory function [3].

J. Morera (✉)
Department of Endocrinology and Diabetology, Caen University Hospital, Caen, France
e-mail: morera-j@chu-caen.fr

Table 1: Comparison of advantages and disadvantages of vial/syringes and reusable and prefilled insulin pens [2].

	Advantages		**Disadvantages**	
Vials and syringes	Reduced cost per unit of insulin Up to 100 U in one injection Half-increment dosing Patients can mix their own insulin formulations		More fear of injections Poor dose accuracy Lack of social acceptance Lengthy training time Difficulty of transportation No short needles	
Insulin pens	Ease of use Greater social acceptance/discretion of use Ease of portability Improved treatment adherence Less painful Short needles		Need for two injections in the case of high insulin doses (>60 or 80 U) Patients cannot mix their own insulin formulations Significant cost per unit of insulin	
	Prefilled insulin pen Easiest to use Lighter than a reusable pen	*Reusable insulin pen* Better environmental impact Possible memory function Half-increment dosing	*Prefilled insulin pen* Possible involuntary mixing between the long-acting and rapid-acting analog insulin pens	*Reusable insulin pen* Heavier than a prefilled pen

These innovations have led to pen devices being used by approximately 60% of insulin users worldwide [4], though there are disparities between different countries: in European countries, Japan, China and Australia, pen devices are used by 95% of insulin users, whereas in the U.S.A., they are used by only approximately 60% of patients [1].

Patients prefer the pen devices to vials and syringes, stating advantages such as ease of use (even in cases of impaired vision or compromised manual dexterity), convenience, greater confidence in their ability to properly administer the drug, less pain and less needle fear, and greater perceived social acceptance [2, 3], especially if they feel encouraged by their physicians to use a pen [5]. Patients also seem to take less time to learn to inject themselves with a pen compared with a syringe [2].

Insulin analogs supplied in cartridges or prefilled pens have a higher per-unit insulin cost than do insulin analogs supplied in vials [6], but a review [7] showed that use of pen devices was associated with improved adherence to insulin therapy and in this way reduced diabetes care costs compared with vials and syringes [6, 7].

Prefilled Versus Reusable Insulin Pens

There are two types of insulin pens:

- Reusable insulin pens which are designed for use with 3-ml prefilled insulin cartridges and are listed in Table 2 (nonexhaustive data). These pens may be preferred for environmental reasons but also in pediatric population and in patients with small insulin requirements because some of them offer the possibility for half-increment dosing.
- Prefilled insulin pens which contains 3 ml of insulin and are listed in Table 3.

Table 2: List of reusable insulin pens actually marketed (nonexhaustive data).

	Traditional reusable insulin pens													Connected reusable insulin pens		
	ClikStar	JuniorStar	HumaPen Luxura HD	HumaPen Savvio	HumaPen Memoir	NovoPen® 4	NovoPen® 5	NovoPen® Echo	Diapen Softpen	I-pen	AutoPen		AutoPen24	DataPen	SmartPlus Digital	VigiPen®
Pharmaceutical laboratory	Sanofi		Lilly			Novo Nordisk			Haselmeier		Owen Mumford			Biocorp	SmartPlus	Vigilant
Insulin	Glargine Glulisine		Humulin Lispro Biphasic lispro			NPH Aspart Biphasic aspart Detemir			All insulin		Sanofi cartridges		Lilly cartridges	All insulin cartridges	Sanofi and Lilly cartridges	Rechargeable VigiPen® cartridges with all bottled insulin
Max units (U)	80	30	30	60		60		30	58	60	21	42	21	42	ND	60	21
Min units (U)	1	1	0.5	1		1		0.5	1	1	1	2	1	2	ND	0.5	1
Dose increment (U)	1	0.5	0.5	1		1		0.5	2	1	1	2	1	2	ND	0.1	1
Duration of press on button (s)	10		5			6			ND		10		10		ND	ND	ND
Specific features	–	–	–	–	Memory function display	–	Memory function display	Memory function display	Automated needle insertion and dose delivery Hidden needle	–	Automated dose delivery at touch of button		–		Software: ND	Software: DiabeticPlus (Apple or Google Play)	Software: VigiHealth app (Apple or Google Play)

Max maximum, *Min* minimum, *ND* no data, *NPH* neutral protamine Hagedorn (isophane)

Table 3: List of prefilled insulin pens.

	SoloStar®	FlexPen®	FlexTouch®	Innolet®	Kwickpen®
Pharmaceutical laboratory	Sanofi	Novo Nordisk			Lilly
Insulin	Glargine Glulisine	Detemir NPH Aspart Biphasic aspart		Detemir NPH	Humuline NPH Biphasic humuline Lispro Biphasic lispro
Max units (U)	80	60	80	50	60
Min units (U)	1	1	1	1	1
Dose increment (U)	1	1	1	1	1
Duration of press on button (s)	10	6	6	–	5
Features		A dose larger than that remaining in the pen is not possible	Low injection force End-of-dose click	Specifically developed for people with poor eyesight or reduced manual dexterity	

Max maximum, *Min* minimum, *NPH* neutral protamine Hagedorn (isophane)

The choice of insulin pen essentially depends on the choice of insulin and on the patient's preferences (Table 1).

Accuracy of Dosing and Force Required for Insulin Injection

All insulin pens meet International Organization for Standardization (ISO) 11608-1: 2000 standards for dose accuracy at 1 unit: the calculated statistical tolerance limit should not deviate from the target dose by more than 1 unit for the delivery of 5 units and not by more than 5% for the delivery of 30 U and 60 U [8].

Several studies have investigated dosing accuracy among pens and have demonstrated consistent and accurate dose delivery for prefilled and reusable insulin pens according to the ISO recommendations, without clinically relevant differences among the products [9–12].

The force required to inject an insulin dose can also differ between insulin pens, but the study results are conflicting and the observed differences seem relatively small [4, 13–15].

Needle Features

Pen needles come in lengths ranging from 4 to 12.7 mm.

Reduction of needle wall thickness allows the insulin flow to be increased at a constant thumb force, leading to performing an insulin injection more easily and quickly. Extra-thin-wall needles (4 and 5 mm) have been developed and patients who have tested them reported a significant

preference for these needles, describing reduced thumb force, reduced pain and a decreased time to deliver insulin [16].

Furthermore, the 4- or 5-mm needles have a lower risk of intramuscular injection [17] (Fig. 1) and they provide glycemic control equivalent to that of the longer needles, even in obese patients, without an increase in leakage [18–20]. In Europe, 63% of adult patients on insulin treatment were using an 8-mm or longer needle [21]. Future guidelines will recommend greater use of shorter-length pen needles for patients with diabetes.

Trends in Insulin Pen Development

The current trend is the development of insulin pens with an electronic dose display and a memory function. These devices allow the user to record insulin doses and the date(s) and time(s) of the last injection(s), but there is actually no proof that use of this device is associated with an additional improvement in glycemic control [22]. This function can be particularly useful in younger patients in whom insulin is administered by multiple caregivers and it may help reduce the risk of double injections or provide parents with information on a child's adherence to treatment. In a pediatric population, 89% of patients evaluated this function as having good ease of use [23].

In the future there will probably be marketing of connected insulin pens which will, in connection with a mobile application via Bluetooth, allow the patient to track his treatment, improve his adherence and send his data to his doctor (Table 2). Alerts indicating forgotten or inadequate-dose injections could also be an interesting option, since an increase in hemoglobin A_{1c} (HbA_{1c}) of 10% has been estimated for every four missed meal boluses per week in pediatric patients, and an HbA_{1c} effect of −0.5% for only two boluses per week not missed has been estimated [24]. These devices have not yet been evaluated.

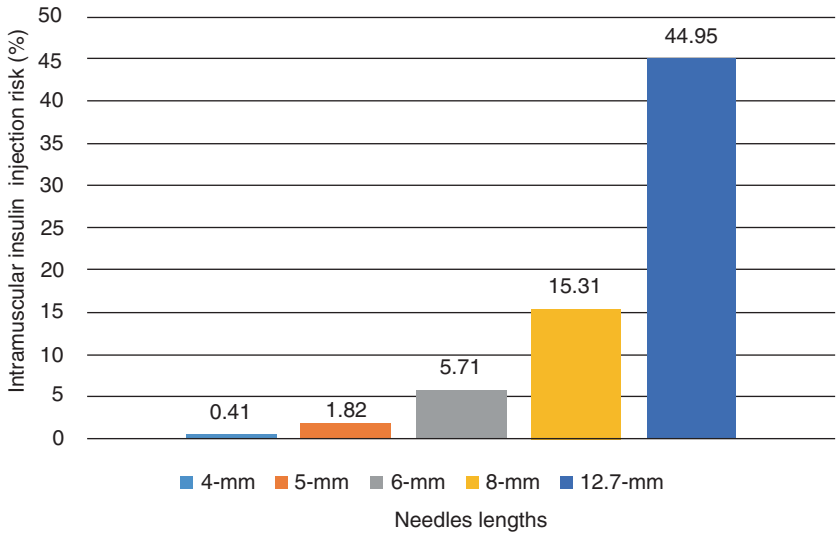


Fig. 1: Risk of intramuscular insulin injection as a function of the length of pen needles (according to [17]).

Medical Devices Associated with Insulin Pens

- Tracking of the Last Injection

There is a smart cap (Timesulin™) that can be placed onto the insulin pen and can display when the last insulin injection was administered. This device is compatible with almost all refillable insulin pens.

- Connected Devices

Medical devices that adapt to insulin pens (Bee™, EasyLog™) are in development and allow the user to record the injected insulin doses and to send these data to a mobile application in order to note them in a glycemic logbook. These devices are compatible with almost all reusable and prefilled insulin pens. However, the glycemic results have to be manually noted in the logbook.

In the future this kind of device will probably be connected to the blood glucose (BG) meter in order to automatically transfer and record the insulin doses and the glycemic data in the same logbook.

- Devices to Use in Cases of Needle Phobia

There are several specific devices with a hidden needle allowing the user to perform insulin injections in people suffering from a fear of needles:

  - BD Autoshield™ Pen Needle (BD; 5 or 8 mm) and NovoFine® Autocover (Novo Nordisk; 8 mm) are pen needles which are applied to the skin, allowing the shield to retract and the hidden needle to penetrate the skin. These devices are compatible with all insulin pens.
  - Novopen® 3 PenMate® (Novo Nordisk) is a device which is screwed onto the body of the insulin pen and wherein an insulin cartridge is inserted. The pen needle is hidden by the device and penetrates the skin after pressure on the body of the insulin pen. It is only compatible with old reusable insulin pens (NovoPen® 3, NovoPen® 3 Demi, NovoPen® Junior) and NovoFine® pen needles.

Insulin Injector

By using a compressed gas cartridge or a compressed spring, needle-free insulin administration devices, such as InsuJet™ and Injex30™, push the insulin at high speed through a small orifice, creating a fine stream of insulin that penetrates the skin (transdermal administration) then diffuses in the subcutaneous tissue. These devices have been developed for needle-phobic diabetic patients.

In healthy volunteers, it has been shown that a jet injector greatly enhances the rate of insulin absorption and reduces the duration of the glucose-lowering action, in comparison with conventional insulin administration, when using insulin aspart [25] or insulin lispro [26], but there has been no study with long-acting insulin analogs.

In a small pilot study of ten patients with type 1 diabetes (T1D), the administration of insulin aspart by an injector had the same effect on the glucose profile as conventional insulin administration and this device was rated similarly for participant preference and relative injection pain [27]. There has been no more extensive study.

The large size, the very high pressure required and the pain induced are reasons why this kind of device has never been a commercially reality. Another limitation is the cost: limited reimbursement in the U.S.A. has deterred many from trying these devices, while in Europe these devices have not been widely promoted within public health systems, except in the UK.

Injection Technique

Practical Aspects

Syringes and pen needles have to be used only once in order to limit the risk of infection and appearance of air bubbles which can lead to underdelivery of insulin. Furthermore, a higher rate of needle reuse has been identified as an independent risk factor for lipohypertrophy [28].

Pens must be primed before each injection with 2 units of insulin in order to displace any air in the needle and to ensure an accurate injection avoiding underdelivery of insulin, even if the pen needle is changed.

For an insulin pen, the needle should be embedded within the skin for several seconds after complete depression of the plunger to ensure complete delivery of the insulin dose. In cases of premature needle withdrawal after injection, there may be a non-negligible amount of insulin not delivered (up to 20% of the selected dose) and this can be critical for subjects with low insulin needs [29], but this phenomenon can be avoided by keeping the needle in the skin as recommended by the manufacturer (Tables 2 and 3).

Injection Sites

Insulin injections have to be administered in subcutaneous tissue (in the abdomen, buttocks, lateral sides of thighs and upper arms). Intramuscular injection should be avoided due to the risk of severe hypoglycemia [30]. Since the 4-mm pen needles were introduced, other insulin injection sites have been explored and the upper inner thigh might be another option [31].

Site rotation is essential to avoid lipohypertrophy and ensure consistent absorption of the insulin. Patients should be taught a personalized "structured rotation" for their injection sites.

Structured rotation is recommended in the same anatomical region at the same time of day with the injections being at least 2–3 cm apart (two fingers) across the entire area (Fig. 2).

Conclusion

The evolution of insulin devices has allowed us to improve patients' comfort and technological advances now make it possible to personalize the choice of assistance devices for each patient, while ensuring better performance on the part of these devices. In the future, connected and painless devices will probably be developed and should be made available to patients to improve their adherence to antidiabetic treatments.

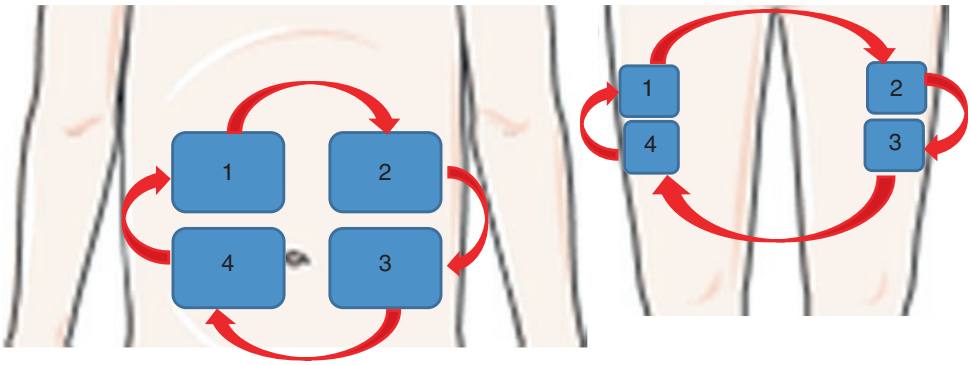


Fig. 2: Sample structured rotation plan for injections in the abdomen and thighs: divide the injection side into quadrants or halves, use one section per week and move clockwise. Injections within any quadrant should be spaced at least 2–3 cm from each other.

Blood Glucose Meter Systems

Self-measurement of blood glucose (SMBG) is an essential element in the treatment of patients with T1D and insulin-treated type 2 diabetes (T2D), allowing the patient to adjust insulin therapy in order to have tight glycemic control and avoid late complications [32, 33]. Its use is more controversial in non-insulin-treated patients with T2D but can help to evaluate the efficacy of hypoglycemic treatments and play an educational role for patients [34, 35].

Since the first BG meter was manufactured in 1970, many improvements have been made, leading to the current BG meters which have become lighter, faster in determination of glucose values, easier to use, with a reduced deposit volume needed to determine capillary BG.

In parallel, lancing devices have been modernized, becoming less painful, mainly for obtaining a lesser quantity of capillary blood (0.3–0.5 µl) [36].

Principle of Glucose Detection

Glucose meters have two essential parts: an enzymatic reaction and a detector. The enzyme portion of the glucose meter is generally packaged in a rehydrated state in a disposable strip. Glucose in the patient's blood sample rehydrates and reacts with the enzyme to produce a product that can be detected. There are two principal enzymatic reactions utilized by glucose meters: glucose oxidase (GO) and glucose dehydrogenase (GDH) [37].

The GO method involves the oxidation of glucose to gluconic acid by GO, forming hydrogen peroxide. This reaction is not completely specific for glucose and can give falsely low results with high oxygen content or substances such as uric acid, ascorbic acid, bilirubin, hemoglobin, tetracycline and glutathione [38].

The GDH method involves the oxidation of glucose to gluconolactone by GDH, forming reduced nicotinamide adenine dinucleotide (NADH) [38].

All meters are susceptible to heat and cold because the enzymes can be denatured and become inactivated at extreme temperatures. Test strips should not be stored in closed vehicles for extended periods and must be protected from rain, snow and other environmental elements [39].

A number of factors can cause erroneous readings on BG meters and these aspects have to be taken into account in order to choose the best BG meter for each patient:

- With the GO method of detection, an increase of the glucose reading can be observed in the case of anemia, low oxygen content, alkalosis or overdose of paracetamol, while a decrease can be observed in the case of polycythemia, high oxygen content, acidosis or overdose of uric acid, ascorbic acid or tetracycline.
- With the GDH method detection, an increase of the glucose reading can be observed in cases of anemia, products containing xylose, hyperbilirubinemia or overdose of paracetamol, while a decrease can be observed in cases of polycythemia, hypercholesterolemia (>11 g/l) or hypertriglyceridemia (>47 g/l) [39].

However, these factors actually have little bearing in the average patient with diabetes mellitus, and human misuse of the BG meter has been found to be a more significant source of error than the instrument itself [40].

Accuracy and Security

Technical Accuracy

Technical accuracy is defined as the measurement closeness of agreement between a measured quantity value and a true quantity of glucose. This criterion is different from precision which describes the reproducibility of a series of values, independent of the closeness of any of the values to the reference (Fig. 3) [39]. Only when a series of values is both accurate and precise do the individual values reflect the reference value.

Fig. 3: Accuracy and precision of glucose meters. In *each panel*, the *center of the circle* represents the reference value. In the *left panel*, the individual values have a mean value that is the same as the reference value, defining the accuracy. In the *center panel*, all values are nearly identical, defining the precision. In the *right panel*, the set of values is both accurate and precise [39].

There are a number of factors that can influence the accuracy of BG strips [39]:

- Variation of the strip's quality between different manufactured lots
- Influence of altitude
- Influence of extreme temperature
- Variation of the hematocrit level which can change the glucose reading but can also block the electrode or the enzyme of the strip and alter the reading
- Patient technique
- Use of some medication

Clinical Accuracy

While technical accuracy refers to the analytical result agreement of a BG meter with a comparative laboratory method, clinical accuracy compares the medical decisions based on the test results.

Clarkes [41] and then Parkes [42] established error grid analysis in order to evaluate SMBG methodologies and verify the clinical significance of the BG meter result against a comparative method. These error grids have five accuracy categories: zones A and B for when we can see a mild discrepancy between the glucose meter result and the comparative method, resulting in no change in the clinical decision; and zones C, D and E for when we can see larger differences between the glucose meter and the comparative method, resulting in unnecessary corrective action or potentially dangerous failure to detect hypoglycemia or hyperglycemia (Fig. 4).

Meter Performance Criteria

Manufacturers of glucose meters have to provide evidence of conformity with the ISO 15197:2013 standard [43] which defines the following performance requirements for glucose meters:

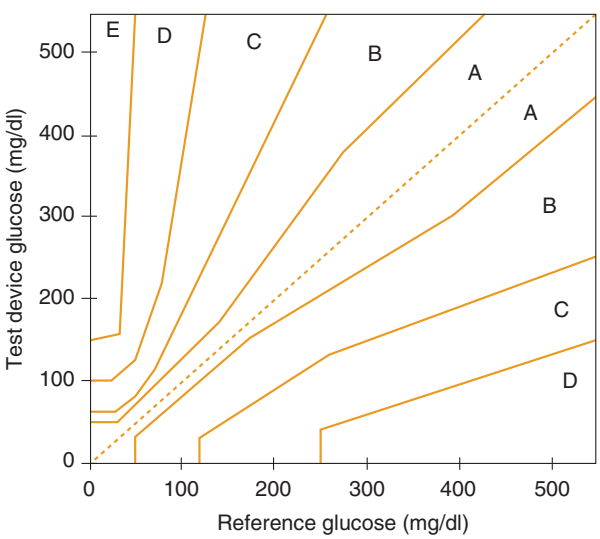


Fig. 4: Parkes error grid. The error grid is divided into zones signifying the degree of risk posed by incorrect measurement: A: no effect on clinical action; B: altered clinical action or little or no effect on clinical outcome; C: altered clinical action—likely to affect clinical outcome; D: altered clinical action—could have a significant medical risk; E: altered clinical action—could have dangerous consequences [42].

- The standard states that ≥95% of the BG system measurement results shall fall within ±15 mg/dl of the results of the manufacturer's measurement procedure at glucose concentrations <100 mg/dl and within ±15% at glucose concentrations ≥100 mg/dl.
- Ninety-nine percent of individual glucose results shall be included in zones A and B of the Parkes error grid.
- Evaluation of interferences is mandatory, with a list of 24 substances which need to be tested. The influence of the hematocrit on the glycemic level shall also be studied.

Criteria for Choosing a Glucose Meter

Some examples of BG meters are listed for each selection criterion, but the list is not exhaustive. Depending on the country, the names of BG meters may be different from those used in this text.

Patients with Type 1 Diabetes

Use of an Automated Bolus Advisor

Bolus insulin calculation requires individuals to utilize several factors such as insulin to carbohydrate ratios, the insulin sensitivity factor, target BG range, current BG values and anticipated physical activity. This calculation can be problematic in individuals with deficits in literacy and numeracy, and can be replaced by an empirical estimate of the insulin need because the calculation is complex and time consuming. The use of an automated bolus advisor can facilitate improvements in glycemic control without increasing hypoglycemia, improve treatment satisfaction, reduce dosage errors, assist in improving carbohydrate counting competence and reduce fear of hypoglycemia [44]. Only the FreeStyle Papillon® InsuLinx BG meter (Abbott) has this device.

Blood Ketone Detection

Measurement of whole-blood or urinary ketones plays an important role in the management of diabetes ketoacidosis. Ketone meters are often available in emergency rooms but can be prescribed to patients with brittle glycemic control in order to detect, as early as possible, the presence of ketones in the case of hyperglycemia and start corrective measures.

This ketone meter concerns patients with T1D exposed to a ketoacidosis risk—in particular:

- Children and teenagers
- Patients treated with an external or implantable insulin pump
- Pregnant diabetic women
- Young patients with behavioral disorders that can lead to noncompliance with insulin therapy [45]

The FreeStyle Optium® Neo meter (Abbott; FreeStyle Optium® β-ketone strips) and the Glucofix® Premium meter (Menarini; Glucofix® β-ketone sensor strips) are BG meters using this function.

Connection with a Subcutaneous Insulin Pump

Use of an automated insulin pump and meter seems to increase the daily frequency of BG testing in youth patients with T1D [46].

The Contour Next® Link meter (Bayer) connects to the Medtronic MiniMed® Real-Time and MiniMed® Veo pumps and the Contour Next® Link 2.4 m connects to the Medtronic 640G® pump. These BG meter can directly transfer the glycemic results to the pump and, in some cases, be used to program a bolus. The uploading of pump data also allows a display of insulin doses and BG results in the same graph or the same table (see example using the Contour Next® Link BG meter and the MiniMed® Veo pump in Fig. 5).

Patients with Type 1 Diabetes or Type 2 Diabetes Receiving Multi-daily Insulin Injections

Presence of a Logbook in the Blood Glucose Meter

This device can help patients to fill out a correct glycemic book (FreeStyle Papillon® InsuLinx BG meter). Indeed, we know that in one study only 58% of people with T1D reported they performed

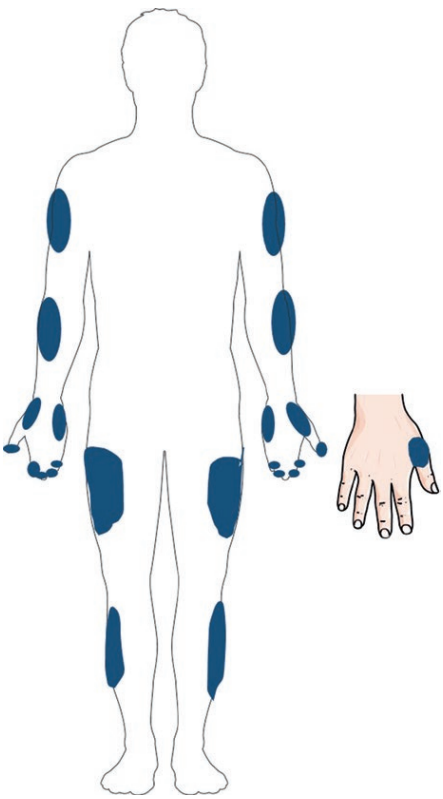


Fig. 5: Alternative sites for the capillary glucose test.

at least three tests a day [47] and all these results are not always recorded in a glycemic book or are not in agreement with the meter memory in 50% of cases, because of underreporting, lack of concordance or overreporting [48].

No Strip

Self-measurement of blood glucose is time consuming which can decrease the frequency of BG testing.

The Accu-Chek® Mobile (Roche) is an all-in-one meter and allows the user to perform BG measurement faster and more easily. Indeed, the single strips are eliminated, with 50 strip-free tests on a continuous tape and the integrated lancing contains six lancets in a drum, requiring only four steps to perform a test.

The FreeStyle Libre® (Abbott) is a continuous glucose monitoring device coupled to a meter able to scan and store glycemic results. This system allows the user to know the glucose level without a strip or lancing device. It is faster and more painless than traditional SMBG.

Alarm Function

Blood glucose meters can have an alarm function in order to remind the patient to perform a BG measurement (FreeStyle Papillon® BG meters, Contour BG meters, Accu-Chek® BG meters, Glucofix® Tech meters, etc.). This can be useful for patients who tend to forget to measure their capillary glycemic level. There are two types of alarms:

- A postprandial alarm function to inform the patient that it is time to measure their postprandial glucose level
- A programmable alarm that is set by the patient for the desired time

Connection with a Smartphone

Some BG meters can be connected with a smartphone. Free downloaded apps are needed in order to edit the glycemic data in logbooks, tables or graphs and statistic reports, and these reports can be sent to the user's physician by email. The transfer of data is possible either when the BG meter and smartphone are physically connected or via Bluetooth transmission. The following are some BG meters:

- iBGStar® meter (Sanofi) which connects to an iPhone or iPod only and requires the iBGStar® Diabetes Manager application, only available from the Apple Store
- Glucofix® Tech meter (Menarini) which connects to a smartphone (or tablet) and requires the GlucoLog® Lite or GlucoLog® Mobile applications, available from the Apple Store or Google Play
- OneTouch Verio® Flex meter (LifeScan) which connects to a smartphone (or tablet) and requires the OneTouch Reveal® application, available from the Apple Store and Google Play

Continuous Glucose Monitoring

The FreeStyle Libre® is based on a flash glucose monitoring system. It uses a small sensor which automatically measures and stores the glucose results, coupled to a meter which reads the glucose result by scanning even through clothing. The sensor is small (35 mm × 5 mm), is water resistant, is applied on the body once every 2 weeks and does not require finger pricks for calibration. With every scan, the current glucose reading is obtained but also an arrow showing the glycemic trend and the last 8-h of glucose data are shown as a graph. The system stores up to 90 days of glucose data.

The performance of this system was demonstrated in a study showing accuracy in comparison to capillary BG reference values and stability of accurate readings over 14 days of use, and the percentage of readings within consensus error grid zone A was between 85.2% and 89.2% [49].

The data can be transferred to a computer via FreeStyle Libre® software and are summarized as a graph (Ambulatory Glucose Profile).

Patients with Type 2 Diabetes Receiving Multi-daily Insulin Injections or Only Basal Insulin

Assistance in Interpretation of Results

Blood glucose meters offer the possibility to help the patient to interpret his glycemic result, either:

- With an alert in the case of hypo- or hyperglycemia (BGStar®, Sanofi; OneTouch Verio® and OneTouch Verio® Flex; AutoSense®, Aximed).
- With an indication of a glycemic trend over several days. This indication can be noted by trend arrows (FreeStyle Optium® Neo; MyStar® Extra, Sanofi) or by a color code (OneTouch Verio® IQ, LifeScan). One study compared the efficacy of the self-management performance of two color-indication methods, with one group of patients recording their BG levels on the note manually and marking high and low levels with red or blue pencil, respectively, and another group using a BG meter with color-coded indicator lights (red, orange, green and blue lights) signifying BG levels [50]. The manual color record seemed to have a favorable effect, resulting in improved glycemic control and suggesting active usage of the glycemic results.

Non-insulin-treated Patients with Type 2 Diabetes and Patients with Gestational Diabetes

Almost all patients look for simplicity of use and prefer BG meters which do not require calibration. The criteria for choice are more oriented toward BG meter design, size or simplicity of use.

Other Criteria for Choice of Meters

Eye Disorders

If the disease is moderate, it can be useful to focus on a BG meter with a large screen and large displayed letters (FreeStyle Papillon® Vision, Abbott; Glucofix® Premium and Glucofix® ID, Menarini;

Accu-Chek® Performa, Roche) or with a display backlight (OneTouch Verio®; BGStar®; MyLife® Pura, Yposmed).

In the case of blindness, a talking BG meter can allow the patient to perform glucose measurement by vocalizing each step of the glucose test (AutoSense® Voice, Aximed; Vox®, Os Care). Clear and simple sentences expressed by a human voice indicate the process and guide users from the beginning to the end of the test and clearly set out the results. Different languages are available for each BG meter.

Gripping Disorders

Patients will prefer big BG meters using large and rigid strips, such as MyLife® Pura. The Accu-Chek® Mobile BG meter can also be useful because the operations can be done with only one hand.

In these patients, the use of lancing devices for single use can facilitate obtaining a blood drop (BD Microtainer® lancets, BD; Unistik® 3 Gentle lancets, Owen Mumford). Indeed, these lancing devices are often large, easy to use and usable with one hand because they simplify the test.

Use of Alternative Sites

The majority of BG meters offer the possibility to perform capillary glycemic measurement at different sites, such as the base of the thumb, forearm, upper arm, thigh and calf (Fig. 5), allowing the fingertips to be rested.

Batteries

The energy consumption by BG meters is uneven and depends on the patient's use. The number of batteries differs between BG meters: one or two lithium batteries or two AAA batteries. Some BG meters can be recharged by mains connection.

Storage Capacity and Calculation of Mean Blood Glucose

All BG meters have storage capacities (from 250 to 2000 tests) and almost of them offer the possibility to calculate the mean BG level over the last 7, 14, 30, 60 or 90 days, but these criteria do not seem to be very discriminating factors.

Data Management

All BG meters offer a download function for collecting the glucose data stored in memory, allowing the user to:

- Create a custom folder
- Edit reports, tables and graphs from the downloaded data
- See the glycemic logbook over fixed periods

- Store virtually unlimited data
- Send data to the doctor

Almost all glucometers allow the user to manage the data with specific software which is freely available for download or directly integrated into the BG meter. Connection of the BG meter to the computer can be done by use of a USB cable (which can be attached to a USB port on the BG meter) or infrared adapter (which may or may not be free and is available to order online or included in the BG meter kit).

Some BG meters can be connected to a smartphone via a mobile application to manage the stored data (see above).

There is also nonspecific data management software available for purchase. It is compatible with almost BG meters and some insulin pumps:

- Diabass® software (compatible with PC)
- Sidiary® software (compatible with PC and with Android, iPhone and Windows phones)
- Diasend® software (compatible with PC and Mac)
- Glooko® software (compatible with Android, iPhone and Windows phones)

Conclusion

The self-measurement of blood glucose that has developed during the past three decades has become an essential part of the treatment of diabetes mellitus. The evolution of blood glucose meters has allowed us to improve patients' comfort and technological advances now make it possible to personalize for each patient the choice of assistance devices, while fulfilling the greater performance requirements of these devices.

References

1. Perez-Nieves M, Jiang D, Eby E. Incidence, prevalence, and trend analysis of the use of insulin delivery systems in the United States (2005 to 2011). Curr Med Res Opin. 2015;31:891–9.
2. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol. 2010;4:522–31.
3. Anderson BJ, Redondo MJ. What can we learn from patient-reported outcomes of insulin pen devices? J Diabetes Sci Technol. 2011;5:1563–71.
4. Perfetti R. Reusable and disposable insulin pens for the treatment of diabetes: understanding the global differences in user preference and an evaluation of inpatient insulin pen use. Diabetes Technol Ther. 2010;12:S79–85.
5. Rubin RR, Peyrot M. Factors affecting use of insulin pens by patients with type 2 diabetes. Diabetes Care. 2008;31:430–2.
6. Selam JL. Evolution of diabetes insulin delivery devices. J Diabetes Sci Technol. 2010;4:505–13.
7. Asche CV, Shane-McWhorter L, Raparla S. Health economics and compliance of vials/syringes versus pen devices: a review of the evidence. Diabetes Technol Ther. 2010;12:S101–8.
8. International Organization for Standardization. ISO 11608-1: 2014. Needle-based injection systems for medical use—requirements and test methods. http://www.iso.org/iso/home/store/catalogue_ics/catalogue-detail-ics.htm?csnumber=65021. Accessed 15 Dec 2014.
9. Krzywon M, van der Burg T, Fuhr U, Schubert-Zsilavecz M, Abdel-Tawab M. Study on the dosing accuracy of commonly used disposable insulin pens. Diabetes Technol Ther. 2012;14:804–9.
10. Bohnet J, Schmitz M, Kamlot S, Abdel-Tawab M. Dosing accuracy and insulin flow rate characteristics of a new disposable insulin pen, FlexTouch, compared with SoloStar. J Diabetes Sci Technol. 2013;7:1021–6.
11. Friedrichs A, Basso N, Adler S. Dose accuracy of the ClikStar, NovoPen 4 and Luxura insulin pens: results of laboratory and field studies. J Diabetes Sci Technol. 2011;5:1179–84.

12. Hänel H, Weise A, Sun W, Pfützner JW, Thomé N, Pfützner A. Differences in the dose accuracy of insulin pens. J Diabetes Sci Technol. 2008;2:478–81.
13. Asakura T, Seiko H, Kageyama M, Yohkoh N. Dosing accuracy of two insulin pre-filled pens. Curr Med Res Opin. 2008;24:1429–34.
14. Asakura T. Comparison of clinically relevant technical attributes of five insulin injection pens. J Diabetes Sci Technol. 2011;5:1203–9.
15. Friedrichs A, Korger V, Adler S. Injection force of reusable insulin pens: Novopen 4, Lilly Luxura, Berlipen, and ClikStar. J Diabetes Sci Technol. 2011;5:1185–90.
16. Aronson R, Gibney MA, Oza K, Bérubé J, Kassler-Taub K, Hirsch L. Insulin pen needles: effects of extra-thin wall needle technology on preference, confidence, and other patient ratings. Clin Ther. 2013;35:923–33.
17. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin. 2010;26:1519–30.
18. Kreugel G, Keers JC, Kerstens MN, Wolffenbuttel BH. Randomized trial on the influence of the length of two insulin pen needles on glycemic control and patient preference in obese patients with diabetes. Diabetes Technol Ther. 2011;13:737–41.
19. Hirsch LJ, Gibney MA, Albanese J, Qu S, Kassler-Taub K, Klaff LJ, Bailey TS. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Curr Med Res Opin. 2010;26:1531–41.
20. Hirsch LJ, Gibney MA, Bérubé J. Glycemic control, reported pain and leakage with a 4 mm x 32G pen needle in obese and non-obese adults with diabetes: a post hoc analysis. Curr Med Res Opin. 2012;28:1305–11.
21. De Coninck C, Frid A, Gaspar R, Hicks D, Hirsch L, Kreugel G, Liersch J, Letondeur C, Sauvanet JP, Tubiana N, Strauss K. Results and analysis of the 2008–2009 insulin injection technique questionnaire survey. J Diabetes. 2010;2:168–79.
22. Danne T, Forst T, Deinhard J, Rose L, Moennig E, Haupt A. No effect of insulin pen with memory function on glycemic control in a patient cohort with poorly controlled type 1 diabetes: a randomized open-label study. J Diabetes Sci Technol. 2012;6:1392–7.
23. Olsen BS, LilleØre SK, Korsholm CN, Kracht T. Novopen Echo® for the delivery of insulin: a comparison of usability, functionality and preference among pediatric subjects, their parents, and health care professionals. J Diabetes Sci Technol. 2010;4:1468–75.
24. Burdick J, Chase HP, Slover RH, Knievel K, Scrimgeour L, Maniatis AK, Klingensmith GJ. Missed insulin meal boluses and elevated hemoglobin A1c levels in children receiving insulin pump therapy. Pediatrics. 2004;113:e221–4.
25. Engwerda EEC, Abbink EJ, Tack CJ, de Galan BE. Improved pharmacokinetic and pharmacodynamic profile of rapid-acting insulin using needle-free jet injection technology. Diabetes Care. 2011;34:1804–8.
26. Hu J, Shi H, Zhao C, Li X, Wang Y, Cheng Q, Goswami R, Zhen Q, Mei M, Song Y, Yang S, Li Q. Lispro administered by the QS-M needle-free jet injector generates an earlier insulin exposure. Expert Opin Drug Deliv. 2016;13:1203–7.
27. Reutens AT, Balkau B, Cohen N. A pilot study to examine the tolerability and device preference in type 1 diabetes of insulin aspart administered by InsuJet compared with subcutaneous injection. Diabetes Technol Ther. 2014;16:235–40.
28. Al Hayek AA, Robert AA, Braham RB, Al Dawish MA. Frequency of lipohypertrophy and associated risk factors in young patients with type 1 diabetes: a cross-sectional study. Diabetes Ther. 2016;7:259–67.
29. Joubert M, Haddouche A, Morera J, Rod A, Reznik Y. Potential insulin underdelivery from prefilled and reusable insulin pens in cases of premature needle withdrawal: a laboratory evaluation. Diabetes Technol Ther. 2015;17:712–6.
30. Frid A, Ostman J, Linde B. Hypoglycemia risk during exercise after intramuscular injection of insulin in thigh in IDDM. Diabetes Care. 1990;13:473–7.
31. Yuan J, Chen Y, Xuan Y, Cao L, Zhu J, Wang F, Zhou X, Ye Q, Liao L, Zheng Y, Zhou Q, Chen X, Chen M, Zhou W. Can the upper inner side of the thigh become a new option for insulin injection? Curr Med Res Opin. 2016;32:1319–24.
32. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2011;12:11–7.
33. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, Rodriguez H, Simmons JH, Hirsch IB. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care. 2013;36:2009–14.
34. American Diabetes Association. Standards of medical care in diabetes—2016. Diabetes Care. 2016;39(Suppl 1):S1–S112.
35. International Diabetes Federation. Self-monitoring of blood glucose in non-insulin treated type 2 diabetes. http://www.idf.org/webdata/docs/SMBG_EN2.pdf. Accessed 2009.

36. Dufaitre-Patouraux L, Vague P, Lassman-Vague V. History, accuracy and precision of SMBG devices. Diabetes Metab. 2003;29:S7–S14.
37. Tonyushkina K, Nichols JH. Glucose meters: a review of technical challenges to obtaining accurate results. J Diabetes Sci Technol. 2009;3:971–80.
38. Moodley N, Ngxamngxa U, Turzyniecka MJ, Pillay TS. Historical perspectives in clinical pathology: a history of glucose measurement. J Clin Pathol. 2015;68:258–64.
39. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. J Diabetes Sci Technol. 2009;3:903–13.
40. Lewandrowski K, Cheek R, Nathan DM, Godine JE, Hurxthal K, Eschenbach K, Laposata M. Implementation of capillary blood glucose monitoring in a teaching hospital and determination of program requirements to maintain quality testing. Am J Med. 1992;93:419–26.
41. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care. 1987;10:622–8.
42. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. Diabetes Care. 2000;23:1143–8.
43. International Organization for Standardization. ISO 15197: 2013. In vitro diagnostic test systems— requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. http://www.iso.org/iso/catalogue-detail?csnimber=54976. Accessed 14 May 2013.
44. Parkin CG, Barnard K, Hinnen DA. Safe and efficacious use of automated bolus advisors in individuals treated with multiple daily insulin injection (MDI) therapy: lessons learned from the Automated Bolus Advisor Control and Usability Study (ABACUS). J Diabetes Sci Technol. 2015;9:1138–42.
45. Guerci B, Tubiana-Rufi N, Bauduceau B, Bresson R, Cuperlier A, Delcroix C, Durain D, Fermon C, Le Floch JP, Le Devehat C, Melki V, Monnier L, Mosnier-Pudar H, Taboulet P, Hanaire-Broutin H. Advantages to using capillary blood beta-hydroxybutyrate determination for the detection and treatment of diabetic ketosis. Diabetes Metab. 2005;31:401–6.
46. Neylon OM, O'Connell MA, Donath SM, Cameron FJ. Can integrated technology improve self-care behavior in youth with type 1 diabetes? A randomized crossover trial of automated pump function. J Diabetes Sci Technol. 2014;8:998–1004.
47. Lecomte P, Romon I, Fosse S, Simon D, Fagot-Campagna A. Self-monitoring of blood glucose in people with type 1 and type 2 diabetes living in France: the ENTRED study 2001. Diabetes Metab. 2008;34:219–26.
48. Given JE, O'Kane MJ, Bunting BP, Coates VE. Comparing patient-generated blood glucose diary records with meter memory in diabetes: a systematic review. Diabet Med. 2013;30:901–13.
49. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. Diabetes Technol Ther. 2015;17:787–94.
50. Nishimura A, Harashima S, Honda I, Shimizu Y, Harada N, Nagashima K, Hamasaki A, Hosoda K, Inagaki N. Color record in self-monitoring of blood glucose improves glycemic control by better self-management. Diabetes Technol Ther. 2014;16:447–53.

Source: Morera J. (2019) Insulin Injection and Blood Glucose Meter Systems. In: Reznik Y. (eds) Handbook of Diabetes Technology. Springer, Cham. https://doi.org/10.1007/978-3-319-98119-2_2.

5

Treatments with Low Glycaemic Index Diets in Gestational Diabetes

Sangeetha Shyam, Amutha Ramadas

Key Points

- Gestational diabetes mellitus (GDM) is the carbohydrate intolerance that results from maternal inability to cope with increased insulin resistance associated with pregnancy.
- Gestational diabetes mellitus management aims to achieve glycaemic control and promote adequate weight gain in the mother and also improve foetal outcomes.
- Diet is the cornerstone of GDM management.
- Low glycaemic index (GI) or glycaemic load (GL) diets by preventing postprandial glycaemic and insulinaemic peaks, attenuate cardiovascular risks; especially in subjects with obesity, insulin resistance or hyperinsulinaemia.
- Low-GI diets are beneficial only when they comply with current dietary guidelines and therefore require appropriate dietetic supervision.
- Gestational diabetes mellitus subjects on low-GI diets have lower spikes in post-meal glycaemia and are less likely to require the initiation of insulin therapy when compared to those receiving standard diets with higher GI.
- Low-GI diets in GDM may also reduce central adiposity in the foetus.
- Low-GI diets are also likely to benefit GDM women in managing their glycaemia and body weight post-delivery.
- Current evidence raises no safety issues in using low-GI/GL diets in GDM management.
- However, further evidence is required to lend unequivocal support for the benefit of low-GI/GL diets in GDM treatment.

S. Shyam (✉)
Division of Nutrition and Dietetics, School of Health Sciences, International Medical University, No. 126, Jalan Jalil Perkasa 19, 57000 Bukit Jalil, Kuala Lumpur, Malaysia
e-mail: sangeethashyam@imu.edu.my; sangeeshyam@gmail.com

A. Ramadas

Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Jalan Lagoon Selatan, 47500 Bandar Sunway, Selangor, Malaysia
e-mail: amutha.ramadas@monash.edu; amutha80@gmail.com

Keywords: Gestational diabetes mellitus, Diet, Glycaemic index, Glycaemic load, Pregnancy

Abbreviations

GDM	Gestational diabetes mellitus
GI	Glycaemic index
GL	Glycaemic load
T2DM	Type 2 diabetes mellitus
RCT	Randomised-controlled trial
CVD	Cardiovascular disease
SCFA	Short-chain fatty acids

Introduction

Gestational diabetes mellitus (GDM) is defined as the 'glucose intolerance first recognised during pregnancy' [1]. All pregnancies are accompanied by metabolic changes that promote adipose tissue accumulation in early gestation, followed by an increase in insulin resistance to provide adequate nourishment to the foetus [2]. The insulin resistance is accompanied by increased pancreatic insulin secretion to maintain maternal euglycaemia as the pregnancy progresses [2]. Hyperglycaemia results when the maternal insulin secretion is unable to meet the increased insulin demand [1, 3]. Therefore, the pathophysiology of GDM is similar to that of type 2 diabetes mellitus (T2DM); namely, marked insulin resistance and impairment of insulin secretion [4] and associated dyslipidaemia [5]. Thus management of postprandial glycaemia and insulin demand are essential targets for GDM management.

Diet is the cornerstone of GDM management [1, 6]. Dietary management for GDM has the following maternal goals: achieving glycaemic control, ensuring adequate weight gain and appropriate nutritional status. Achieving these goals ensures maternal and foetal health. More intensive medical management and increased surveillance are instituted in women who fail to respond adequately to diet therapy and increases treatment costs [7]. Most importantly, GDM increases long-term health risks for the mother and her offspring [1, 7] posing greater demand on healthcare resources.

Carbohydrates predominantly influence postprandial glycaemic response [8]. Therefore, carbohydrate restriction has historically been the prime focus of dietary management for GDM [1]. Restricting carbohydrates to provide around 45% of the energy is safe in GDM pregnancies [9], though evidence from randomised-controlled trials (RCTs) support the use of diets with reasonably high amount of complex carbohydrates [1]. Low-carbohydrate diets that are high in protein and fat intake, may increase risk for diabetes specifically among pregnant women [6] and can compromise foetal outcomes [7]. In the absence of concrete evidence to favour any particular diet, consensus panels for GDM have no specific recommendation but encourage the adoption of conventional healthy diets [1, 5].

As the role for low-carbohydrate diets is limited by their health concerns, the effect of carbohydrate quality (type) on glucose metabolism and insulin resistance has gathered interest [10]. Emerging evidence suggests that deterioration of glucose homeostasis can be prevented by monitoring both carbohydrate quantity and quality [10]. Concepts of glycaemic index (GI) and glycaemic load (GL) were born out of this need to describe the quality or type of carbohydrate foods.

This review aims to assess the current evidence for the treatment of GDM with low-GI/GL diets. The objective of this review is in-line with the professional societies' repeated calls for the consolidation of current evidence and efforts to bridge the knowledge deficits in this area to identify optimal diets for GDM women [5, 7, 11]. This is especially important because GDM affects a significant proportion of pregnant women globally, and alarmingly its prevalence is increasing [11].

Glycaemic Index (GI)

Carbohydrate foods even when consumed in equal amounts differ in their glycaemic effect. Hence physiological effects of carbohydrates are better described by their in vivo ability to raise blood glucose [12]. GI is such a physiological classification of carbohydrates [12], that ranks them on a scale of 0–100, in accordance to their postprandial glycaemic effect [13]. GI, therefore, reflects the rate of conversion of a carbohydrate into glucose [13]. Higher the GI value of a food, greater the postprandial glycaemic response it elicits [14] (Fig. 1).

The GI of a food is measured as 'the incremental area under the blood glucose response curve of a 50 g available carbohydrate portion of the food expressed as a percentage of the response after 50 g of glucose taken by the same subject' [14]. To simplify interpretation, foods are often classified into three categories based on their GI: high (GI >70), intermediate (GI between 55 and 70) and low (GI <55) [15].

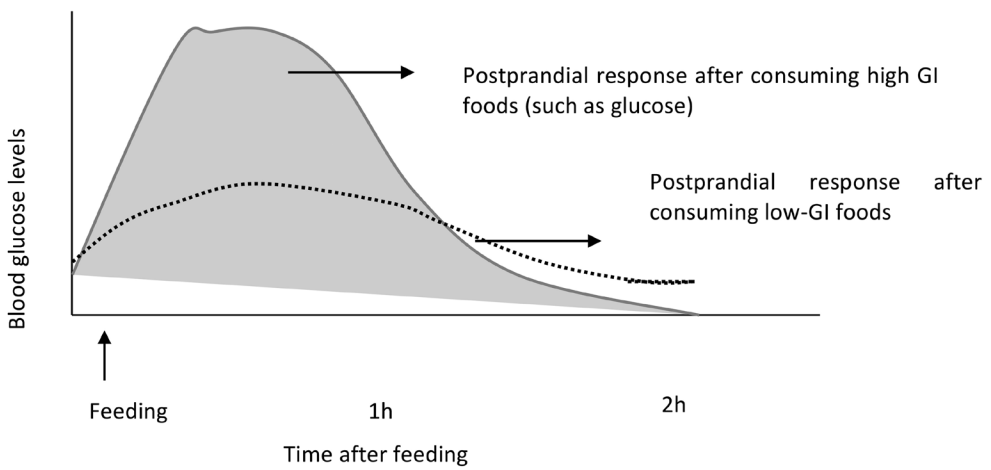


Fig. 1: Comparison of blood glucose *curves* after consumption of low- and high-GI foods. *Legend: GI*: glycaemic index

Factors Affecting Glycaemic Index

The differences in GI of food depend on the type of sugar and or starch it contains [16], the extent of processing it has undergone [15] and the presence of factors that determine the rate of carbohydrate absorption [16]. Low-GI recommendations utilise these determinants to lower postprandial glucose responses.

Foods with a high content of fructose (fruits), and galactose (milk products) provide lower amounts of absorbable glucose, and thus have lower GI [16]. Beans and seeds have fibrous coats that slow down the access of enzymes to the starch inside [17, 18]. Beans and rolled oats are also rich in viscous fibre that delays gastric emptying [19], enzymatic starch hydrolysis [17] and consequently delay glucose absorption [19]. Basmati rice and legumes also contain a greater amylose: amylopectin ratio that slows down the rate of starch hydrolysis and glucose absorption [16]. The presence of organic acids in oranges [20] and legumes [18] reduce the rate of starch digestion and thereby elicit lower glycaemic responses. These foods are therefore recommended in low-GI diets. Small amounts of acetic acid (vinegar) when consumed along with the meal, reduces postprandial hyperglycaemia by 20% due to delayed gastric emptying and inhibition of digestive enzymes [21] and is a probable strategy to reduce meal GI. Furthermore, gelatinization of starch during heat treatment increases its availability to amylases and its GI [22]. Therefore, low-GI recommendations emphasise on the need to prevent overcooking of cereal foods like spaghetti and oatmeal.

Glycaemic Index of Mixed Meals

Glycaemic index of individual foods in a meal has shown to predict the glycaemic response when eaten together [16] in different environments and for different cuisines [23]. The GI of a mixed meal is calculated as the sum of the proportional GI contributions of each carbohydrate component of the meal [16]. Daily diet GI is similarly calculated as the mean GI of meals consumed during the day [18].

A 15% reduction in dietary GI (~10 GI units for most population) is thought to confer clinically significant health benefits [24, 25]. Given that staple cereals predominantly determine dietary GI, a 10 unit GI reduction is achieved by substituting usual high-GI staples with lower GI alternatives, while maintaining their prescribed serving size [26]. Another practical strategy to efficiently lower GI is to include one low-GI food in each meal, since GI works through the principle of averages [24]. A sample of dietary recommendations used to lower the GI of healthy diets is provided in Table 1.

Glycaemic Load (GL)

Due to its methodology of determination, GI may not reflect the glycaemic effect of a typical carbohydrate serving [27]. The glycaemic load (GL) concept was therefore invented to quantify the overall glycaemic effect of a portion of food [28]. The GL of a typical serving of food is the product of the amount of available carbohydrate it contains and its GI value [8]. GL of a serving

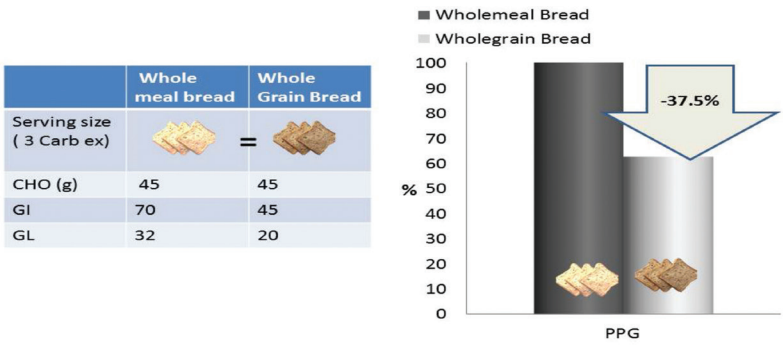
Table 1: Dietary recommendations use to lower dietary GI without causing major macronutrient changes.

Food	Low-GI	Moderate-GI	High-GI
Recommendation	**Encouraged**	**Moderation advised**	**Discouraged**
Cereals and grains			
Rice	Parboiled	Basmati rice, brown rice, white rice with yoghurt (curd rice)	White rice, fragrant rice, Jasmine rice, glutinous rice
Bread	Multi-grain bread	Pita bread, chapatti made from wheat atta with dhal	White bread, wholemeal bread
Breakfast cereal	Muesli, coarse oat bran	Quick cooking/instant oats	Cornflakes, chocolate coated cornflakes, sugar coated cornflakes
Noodle and pasta	Macaroni, fettuccine spaghetti, noodles (al-dente)	Udon noodles plain	Rice noodles (fried)
Biscuits	Cream crackers—high calcium	Digestive biscuits, wholemeal biscuits, oatmeal biscuits	Wafers, sugar coated biscuits
Vegetables	Green peas, carrot, green vegetables	Sweet corn, sweet potato, yam	Pumpkin, tapioca potato
Fruits	Apple, orange, pear, plum, strawberry, dates	Grapes, banana, papaya, mango, raisins, pineapple	Watermelon, lychee
Legumes and nuts	Baked beans, kidney beans, soya beans, chick peas, lentils (dhal), mung beans, dried peas Nuts—though low in GI, moderation is encouraged	–	–
Dairy products	Skim milk, low-fat milk, low-fat yoghurt	Condensed sweetened milk	–

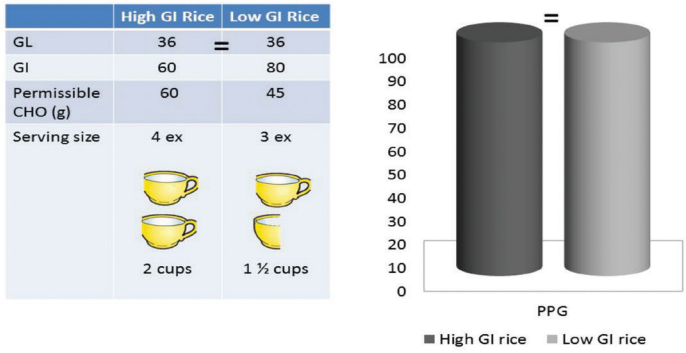
Source Adapted from Shyam *et al*. [86]
Note Serving size recommendations need to be adhered to even when using low-GI options
Legend GI: glycaemic index

is thus a measure of both carbohydrate quality and quantity [8] and accurately predicts postprandial glycaemia [29]. Accordingly, GL of a meal can be reduced either by reducing the amount of carbohydrate in diet, selecting foods that have lower GI or a combination of both [29] (Fig. 2).

While dietary GL can be reduced by different methods (Table 2), efforts that lower risks for T2DM [28] and cardiovascular disease (CVD) [3], reduce GL predominantly by lowering dietary GI, with minimal reduction to carbohydrate (compensated by slightly higher protein) content [29]. Thus, healthy low-GI/GL diets are essentially matched for calories, macronutrient distribution and other aspects of nutritional adequacy afforded by conventional healthy diets. The difference remains in the source of carbohydrates, primarily with respect to staples.



Comparison of the postprandial glycaemic responses of breads varying in GI, when the portion size is maintained constant



Comparison of the potential serving size of rice varying in GI to maintain a constant GL

Fig. 2: Postulated practical application of GL concept. *Legend* GI: glycaemic index, GL: glycaemic load, CHO: carbohydrate amount (g), PPG: postprandial glycaemic response. *Top panel* shows that a similar portion of a lower GI option (wholegrain bread) versus a higher GI option (wholemeal bread) will reduce GL and hence result in lower postprandial glycaemic response. *Bottom panel* shows that theoretically a smaller serving size of a higher GI option (high-GI rice: e.g. glutinous rice) can have a similar GL as a slightly larger serving size of a lower GI option (low-GI rice: e.g. Basmati rice). However the increase in total calories as the number of carbohydrate exchange increases should be considered.

Possible Benefits of Low Glycaemic Index Diets in GDM Management

The advocacy for low-GI foods in promoting health draws from its ability to lower postprandial glycaemic and insulinaemic responses [17]. Chronic consumption of high-GI foods results in marked rise in glycaemia [17], and demands more insulin. This demand is initially compensated by increased insulin secretion [12]. This increased insulin demand exacerbates insulin resistance [12]. Hyperinsulinaemia and insulin resistance that are central to GDM pregnancies [2], eventually lead to β-cell fatigue and increased cardiovascular risks [12] as shown in Fig. 3.

Table 2: Comparing options to lower dietary GL of a sample 1800 kcal diet.

	Sample		**Option A**		**Option B**	
Diet	**Standard healthy diet**		**Low-GI diet option**		**Low-carbohydrate diet option**	
	g	% en	g	%en	g	% en
Carbohydrate	248	55	248	55	**180**	**40**
Protein	90	20	90	20	**68**	**15**
Fat	50	25	50	25	**70**	**35**
Diet GI	65		**50**		65	
Estimated diet GL	160		124		120	
Satisfies dietary guidelines	Yes		Yes		No	
Diet GI classification	Medium		Low		Medium	
Expected magnitude of dietary change	None		Medium		High	

Legend GI: glycaemic index, GL: glycaemic load
Bolded portions in Columns "Option A and B" highlight the changes made to the sample healthy diet to lower dietary GL. To achieve a similar reduction in dietary GL, the low-carbohydrate option increases fat intake and requires the implementation of drastic dietary changes

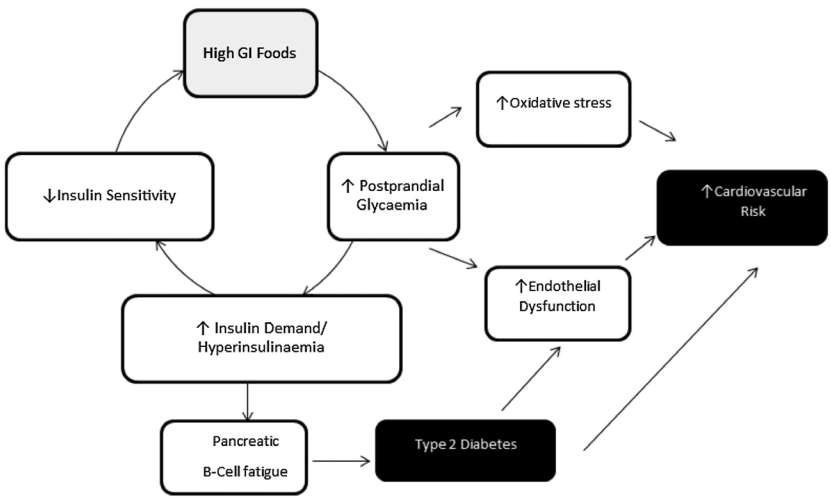


Fig. 3: Potential mechanisms of low-GI diets in the management of glucose homeostasis and cardiovascular risks. Legend: ↑: increase; ↓: decrease, *GI* glycaemic index

In contrast, when compared with high-GI diets, low-GI diets show a slower and more sustained glycaemic response [30]. They prevent exaggerated postprandial glycaemic excursions during pregnancy [31]. Additionally, low-GI meals diminish glycaemic response to the subsequent meal [32]. Besides improving glycaemic control [33], low-GI diets improve insulin sensitivity [34]

and increase β-cell function in individuals with impaired glucose tolerance [35, 36] and T2DM [37]. These actions prevent the degeneration of the glucose tolerance [16] and suggest the potential benefit of low-GI diet in GDM management.

Low-GI foods also lead to the increased secretion of anorexic gut hormones which induce satiety and suppress appetite [39, 40]. Therefore voluntary energy intake is reduced for the rest of the day after a low-GI meal is consumed [41]. Moreover, low-GI diets prevent decreases in fat oxidation induced by hyperglycaemia and hyperinsulinaemia; and increases lipolysis [38, 42]. The postulated mechanisms of action of dietary GI in modulating fat oxidation and body weight gain [42–47] are compiled in Fig. 4. Furthermore, low-GI diets increase protein retention in both normal and hyperinsulinaemic men [48] and favour lean body mass retention [38]. Whether these mechanisms can further optimise body weight management in GDM women, who are more likely to be obese and gain more weight during and after pregnancy [1], remains to be established.

Additionally, low-GI diets by virtue of increased production of short chain fatty acids (SCFA) from colonic fermentation [49], decrease the colonic luminal pH and stimulate the absorption of minerals such as calcium, potassium, magnesium, copper, zinc and selenium [50]. Colonic fermentation also increases folate availability and promotes normal homocysteine concentrations [16, 51]. Colonic fermentation moreover reduces inflammation by altering the bacterial species in the colon [52]. These effects of low-GI diets need to be verified in GDM women.

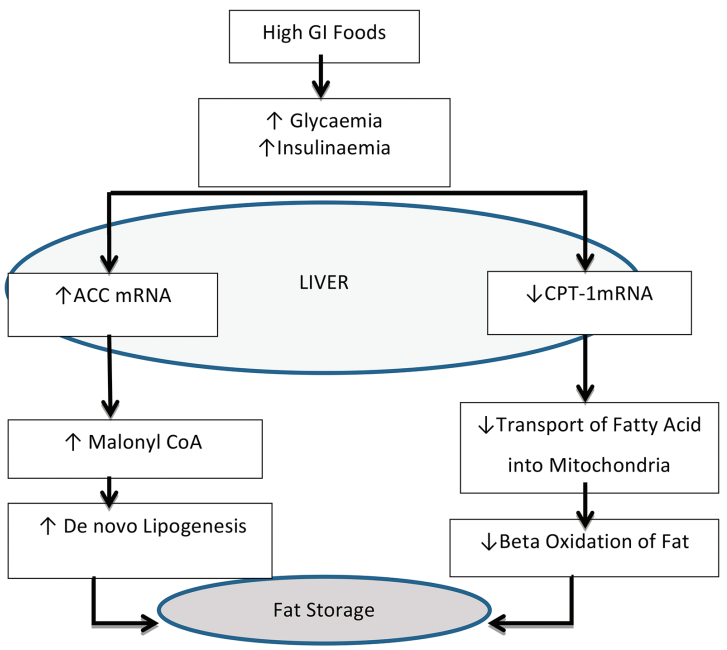


Fig. 4: GI and fat oxidation. Legend: ↑: increase; ↓: decrease, *GI* glycaemic index. High-GI foods reduce hepatic carnitine palmitoyltransferase-1(CPT-1) messenger RNA (mRNA) expression [42]. CPT-1 transport fatty acids into mitochondria for oxidation. High-GI foods concomitantly increase hepatic acetyl-CoA carboxylase (ACC) mRNA expression. ACC catalyses the formation of malonyl-CoA. Malonyl-CoA is a potent inhibitor of CPT-1, resulting in decreased fatty acid oxidation [42, 43]. Thus, high-GI foods lower lipolysis and facilitate fat storage.

Interestingly, low-GI diets are especially beneficial to those with central obesity, insulin resistance, hyperinsulinaemia, diabetes, hypertension and metabolic syndrome [24, 53–56]. In such population, low-GI/GL diet favours weight reduction, glycaemic control and CVD risk reduction, suggesting its potential success in the management of GDM, a condition that shares many of these risks.

In light of the pathophysiological similarities between GDM and T2DM [4], it is pertinent to note that data adds moderate to strong support for the use of low-GI diets in diabetes management [57–60]. The American Diabetes Association grades the evidence to support the substitution of high-GL foods with those with lower GL, to modestly improve glycaemic control in diabetes at "level C" [61].

Current Evidence for the Role of Low Glycaemic Index and Glycaemic Load Diets in GDM Management

For Maintaining or Achieving Glycaemic Control During Pregnancy

Limited evidence supports the effectiveness of low-GI diet in maintaining a good glycaemic control in GDM pregnancies. Only three recent RCTs have investigated the impact of low-GI diet on blood glucose-related parameters [62–64].

Moses *et al.'s* intervention on women with GDM ($n = 63$) at 28 weeks of gestation, found only 29% ($n = 9$) of women receiving low-GI diets required insulin, as compared to 59% ($n = 19$) of women on a conventional-high-fibre-higher-GI-diet [62]. Eventually, 50% ($n = 9$) of these 19 women avoided insulin use after changing to a low-GI diet. However, the final GI of women in both groups were statistically similar and it was noted that increased fibre intake, reduction in carbohydrate intake and self-restriction of energy which occurred in both groups may have interfered with the study outcomes.

Grant and colleagues reported a pilot study ($n = 47$) on the feasibility and effectiveness of a low-GI diet on glycaemic control of GDM women [63]. In contrast to Moses *et al.* [62], Grant *et al.* reported lower dietary GI in the low-GI vs. the control group (49 vs. 58, $p = 0.001$). Improvements in glycaemic control in both groups were reported, but 58% of low-GI group had postprandial glucose within target as compared to 49% of control group ($p < 0.001$). This study was not powered to detect the small difference in self-monitored blood glucose (0.1–0.2 mmol/L) and postprandial blood glucose (1.2 mmol/L) observed between the study groups.

The most recent study by Hu *et al.* [64] was a relatively short 5-day intervention that compared the effectiveness of a low-GI staple versus a normal diabetic control diet among GDM women ($n = 140$) in Guangdong, China. Similar to the earlier studies, postprandial glucose levels were significantly reduced in both groups. However, post-intervention glucose levels taken after each meal were significantly reduced only in the low-GI group. There were also significantly greater reductions in glucose values from baseline in low-GI compared to the control group. The researchers observed a reduction in glucose parameters after breakfast in this group, though low-GI staple foods were only consumed at lunch and dinner. While the generalisability of the

study findings may be limited to Asian women and the feasibility of adhering to a low-GI staple diet can be questioned due to a very short intervention period, the study nevertheless has set a good precedence for future exploration in this area.

Cumulatively these findings suggest that lowering the GI of standard diets by substituting high-GI staples with low-GI options may improve management of glycaemia in GDM women and reduce the likelihood of requiring insulin therapy. This interpretation is further supported by a meta-analysis [65] involving 257 participants that confirmed lesser use of insulin in the low-GI diet group (RR = 0.767, 95% CI = 0.597–0.986, $p = 0.039$) compared to those in control group. This translates into 13 out of 100 GDM women avoiding the use of insulin by adopting a low-GI diet during pregnancy [65].

Prevention of Complications in Pregnancy and Neonatal Outcomes

Foeto-placental overgrowth and higher infant body fat has been associated with high-GI intake during pregnancy, while low-GI diet reduces these tendencies [62, 66]. A small but intensive study by Moses and colleagues [62] showed that the consumption of low-GI diet in the second and third trimesters in normoglycaemic mothers reduced foetal birth weight, foetal percentile and Ponderal index. However PREGGIO, a similar but larger trial [67] found that an early intervention at 20 weeks of gestation did not result in significant differences in similar neonatal outcomes.

Accordingly, Louie *et al*. reported no significant difference in pregnancy outcomes such as birth weight, birth weight centile, prevalence of macrosomia, Ponderal index and adverse pregnancy outcomes after a low-GI dietary intervention that included a minimum of three face-to-face counselling sessions with a dietician [68]. The researchers postulated that a relative small five-point difference in GI between the study groups, early nutrition counselling for both groups, relatively lower GI than norm at the baseline, timing (third trimester) and short duration of the intervention (6–7 weeks) may have contributed to the findings. Another justification for the lack of difference may be the high proportion of participants with normal BMI (68%) and the researchers are now hypothesising low-GI diet to be more efficient among overweight and obese pregnant mothers who have higher level of insulin resistance and deficiency of β-cells [69]. However, it can be concluded that both low-GI and high fibre diet produce optimal pregnancy outcomes and this further strengthens the argument for safety of low-GI diet in the management of GDM.

The significant relationship between maternal glycaemic control and neonatal outcomes has been well-established [70–73]. Higher fasting glucose during initiation of diet therapy was associated with increased neonatal fat mass and elevated C-peptide among women treated for mild GDM in a multicentre RCT [71]. A higher prevalence of elevated C-peptide levels and neonatal outcomes such as macrosomia and large-for-gestational age babies were found among women with higher fasting blood glucose at the final two weeks of gestation. The findings were consistent with an earlier study which described fasting glucose levels to be associated with neonatal adiposity and increased skinfold thickness in neonates, regardless of whether maternal GDM was treated with diet or insulin [72]. Expectedly, secondary analysis of the ROLO study [70] found

low-GI dietary intervention in pregnancy to have a beneficial effect on neonatal central adiposity, which was also positively associated with mother's postprandial glucose. Although the study was conducted among normoglycaemic pregnant women, modest reductions in GI and GL were sufficient to lower neonatal waist: length ratio in the intervention group. This indicates that improved dietary carbohydrate quality may be associated with reduced neonatal central adiposity rather than birth weight. More importantly, epidemiologic studies among healthy pregnant women have found associations between high diet GI and congenital malformations such as neural tube defects, musculoskeletal and gastrointestinal defects [74].

These findings illustrate the importance of carbohydrate quality during pregnancy to promote neonatal well-being. However, while available data indicates the potential role of low-GI diets in reducing fat mass and central adiposity in neonates born to GDM mothers, there is insufficient evidence to establish the benefit of low-GI diets in preventing excessive maternal weight gain, foetal abnormalities, pregnancy complications or adverse pregnancy outcomes.

Prevention of GDM Recurrence and Overt Development of Diabetes

There is limited evidence relating low-GI diets and recurrence of GDM or development of T2DM among women with prior GDM. A recent Asian study [75] among women with prior GDM, compared the effectiveness of low-GI diet and conventional healthy dietary recommendations and reported improvements in glucose tolerance with low-GI educational intervention. The greatest improvement in glucose tolerance was observed among women with higher baseline insulin levels and in the lowest quartile of dietary GI at six months. The researchers also noted a significant reduction in 2-h post-75 g-oral glucose tolerance test (2HPP). In contrast, 2HPP levels increased in the comparison group, resulting in a significant difference in 2HPP changes between groups (Mean difference = 2.4 mmol/L, $p = 0.004$). It was suggested that a reduction of 2HPP by more than 0.84 mmol/L may halve the risk for T2DM and low-GI diet may be able to deliver that especially among women with a history of GDM and higher insulin levels.

In another distinctive study by Ostman and colleagues [76], seven women with impaired glucose tolerance and history of GDM were provided with either low-GI/high-fibre or high-GI/low-fibre bread products, during two consecutive 3-week periods, separated by a three-week washout period. The women receiving low-GI/high fibre bread had 35% lower insulin response to intravenous glucose challenge, though no effect was found on fasting glucose, insulin or lipid markers within the short 3 weeks of intervention. However, the sustainability of the effect remains to be established.

Concerns with the Use of Low-GI Diets

Since its inception, the utility of GI concept has been voraciously debated citing methodological issues and nutritional concerns [18].

Methodological Issues

Among the technical objections, the applicability of GI in mixed meals is predominantly questioned. However, studies reporting a lack of association between GI and glycaemic response when foods are taken as part of a mixed meal [77, 78] are thought to be methodologically flawed [14]. When analysed using standardised methods, the relative glycaemic impact of mixed meals is reportedly predicted by the amount of available carbohydrate they contain and the GI of their components [14].

The practical applicability of GI concept is also limited by the lack of a comprehensive GI database [24, 27]. While the International listing of GI and GL values is indeed comprehensive [13], determination of GI values of local foods is a work in progress in many countries. GI determination is cost and labour intensive and simplified methods have been devised to appropriately match foods and assign GI values to those with unknown values, till more local GI values become available [79]. As many factors affect the GI of a food, including its species, maturity (ripeness), storage time, processing and cooking method, [27], technical uncertainties exist in this estimation process. Estimation of diet GI and GL require in-depth knowledge of carbohydrate intake [16] and food composition tables lack the intricate detail necessary to accurately match foods and their glycaemic response [80]. However, this limitation affects not only the reliability of estimating dietary GI but of all other nutrients as well. Specific biomarkers to assess diet intake, including diet GI, need to be established and will improve the objectivity of dietary assessments.

The relationship between the dietary fibre content and the GI of a food despite being modest [81], confounds existing evidence for the health impact of low-GI diets which are also consistently higher in dietary fibre [27]. While the proponents of GI point to validity and reproducibility of GI values determined in standardised laboratories [29], phenotypic differences among population in response to starch exist [82] and may limit the application of GI values as it is currently determined.

Nutritional Concerns

Nutritional concerns in using GI stem from the fear that it may incite public to consume foods low in GI but high in fat and sugars like ice-cream, cookies, etc. [18, 27, 83]. However, GI proponents argue that GI should be applied only to low-fat starchy foods [84]. GI was never meant to be used in "isolation", but as an adjunct to other healthy eating principles [27]. Therefore the GI concept cannot replace, but should rather supplement existing nutritional strategies [18]. Perhaps the best approach to include GI education in diabetes counselling is to focus on individualisation [83] and this requires appropriate dietetic supervision.

Practical Issues with Implementation

The complexity of the GI/GL concepts make it difficult for patients to comprehend and implement the recommendations [18, 83, 85]. However, many low-GI diet books for weight control and

wellness have been well-received in the West. Whether this acceptance can be extended to the other parts of the globe remains to be answered. Interestingly, various efforts at developing simplified GI-education modules have been successful. Categorising carbohydrates with simple terms like "gushers" and "tricklers" may ease patient comprehension of the concept [17]. Asian RCTs have shown that adults can be counselled to follow low-GI diets without having to memorise GI values [24, 86]. However, these are findings from clinical trials run by trained researchers and the practicality of providing GI-education in conventional healthcare settings remains to be proven.

Another concern with low-GI diets is that it can limit food choices and compromise nutritional adequacy [18, 83]. This may be especially important when dealing with pregnant women. Although traditional Indian and Greek cuisines include more low-GI foods than typical Western diets [83], adopting these food patterns may not be practical for all. Furthermore, food industries face challenges in producing palatable low-GI foods [84]. The issue is further compounded by the absence of a universally accepted logo that would facilitate consumer recognition of low-GI products.

While trials lasting a year or more show similar rates of adherence to low-GI and standard diets across continents [37, 87, 88], feasibility of long-term adherence to low-GI diets is unknown. While it may be possible to plan low-GI diets economically [86], its cost-effectiveness also remains to be established.

Recommendations

While emerging evidence suggests the possible benefit of low-GI diets in GDM management, there is an urgent need for validation of the results. Optimising caloric intake to individual needs, restricting saturated fat, and distributing carbohydrates throughout the day will aid management of body weight and prevent the degeneration of glucose tolerance in GDM women. Dietary recommendations should continue to encourage a moderate carbohydrate diet (45–50%), with adequate dietary fibre (25–30 g). Accordingly, dietary recommendations should encourage the inclusion of whole grains, beans, rolled oats, low-fat dairy and lean meat products, while being mindful of the daily energy needs. These strategies while in-line with conventional dietary goals, will also lower diet GI. Switching to low-GI-staples (such as whole grain breads, low-GI rice varieties and pasta) can be encouraged, taking cues from individual preferences. While adopting low-GI diets, there is a need to continue monitoring the portion sizes since postprandial glycaemia is affected by both the quantity and quality of carbohydrates. Low-GI diets that satisfy other nutritional considerations are acceptable in the treatment of GDM.

Conclusions

Existing evidence suggests that lowering the GI of conventional healthy diets may be beneficial in GDM treatment for managing maternal glycaemia and neonatal adiposity. However, a few practical issues in implementing low-GI dietary recommendations remain unresolved at present. There is an urgent need for adequately powered, well-controlled trials to further investigate the

feasibility, acceptability, adherence, safety, clinical and cost effectiveness of low-GI dietary recommendations in GDM management.

Acknowledgements The authors acknowledge Prof. Dr. Winnie Chee, International Medical University, KL for her guidance while preparing the manuscript.

References

1. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, *et al*. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diab Care. 2007;30(Suppl. 2):S251–S60.
2. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diab Care. 2007;30(Suppl. 2):S112–9.
3. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, *et al*. Glycemic index, glycemic load, and chronic disease risks-a meta-analysis of observational studies. Am J Clin Nutr. 2008;87(3):627–37.
4. Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, *et al*. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA. 1997;278(13):1078–83.
5. Butte FN. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000;71(suppl):1256S–61S.
6. Moses RG, Cefalu WT. Considerations in the management of gestational diabetes Mellitus: "You Are What Your Mother Ate!". Diabetes Care. 2016;39:13–5.
7. Hernandez TL, Anderson MA, Chartier-Logan C, Friedman JE, Barbour LA. Strategies in the nutritional management of gestational diabetes. Clin Obstet Gynecol. 2013;56(4):803–15.
8. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002;76:5–56.
9. Cypryk K, Kaminska P, Kosinski M, Pertynska-Marczewska M, Lewinski A. A comparison of the effectiveness, tolerability and safety of high and low carbohydrate diets in women with gestational diabetes. Endokrynol Pol. 2007;58(4):314–9.
10. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, *et al*. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. New Engl J Med. 2001;345(11):790–7.
11. Different types of dietary advice for women with gestational diabetes mellitus (Review) [Internet]. Wiley; 2013.
12. Augustin LSFS, Jenkins DJ, Kendall CW, La Vecchia C. Glycemic index in chronic disease: a review. Eur J Clin Nutr. 2001;56:1049–71.
13. GI database [Internet]. 2012. Available from http://www.glycemicindex.com. 14. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in Glycemic Index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. Am J Clin Nutr. 2006;83:1306–12.
15. Jenkins D, Wolever T, Taylor R, Barker H, Fielden H, Baldwin J, *et al*. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34(3):362–6.
16. Wolever TMS. The glycaemic index: a physiological classification of dietary carbohydrate. Oxfordshire, UK: CABI Publishing; 2006 227 p.
17. Burani J. Gushers and Tricklers: Practical use of the glycemic index [Powerpoint Presentation]. Marco Island, Florida: University of Sydney; 2006 [cited 2010 11 March]. Available from http://www.glycemicindex.com/glycemic.index.ppt.
18. Kalergis M. The role of the glycemic index in the prevention and management of diabetes: a review and discussion. Can J Diab. 2005;29:27–38.
19. Jenkins DJJA, Wolever TM, Collier GR, Rao AV, Thompson LU. Starchy foods and fiber: reduced rate of digestion and improved carbohydrate metabolism. Scand J Gastroenterol Suppl. 1987;129:132–41.
20. Yoon J, Thompson L, Jenkins D. The effect of phytic acid on in vitro rate of starch digestibility and blood glucose response. Am J Clin Nutr. 1983;38(6):835–42.
21. Johnston CS, Stelewska I, Long CA, Harris LN, Ryals RH. Examination of antiglycemic properties of vinegar in healthy dults. Ann Nutr Metab. 2010;56(1):74–9.
22. Holm J, Lundquist I, Bjorck I, Eliasson A, Asp N. Degree of starch gelatinization, digestion rate of starch in vitro, and metabolic response in rats. Am J Clin Nutr. 1988;47(6):1010–6.
23. Chew I, Brand J, Thorburn A, Truswell A. Application of glycemic index to mixed meals. Am J Clin Nutr. 1988;47:53–6.

24. Yusof BNM. A randomized control trial of low glycemic index against conventional carbohydrate exchange diet on glycemic control and metabolic parameters in type 2 diabetes [Thesis]. Kuala Lumpur: Universiti Kebangsaan Malaysia; 2008.
25. Goff LM, Frost GS, Hamilton G, Thomas EL, Dhillo WS, Dornhorst A, *et al*. Carbohydrate-induced manipulation of insulin sensitivity independently of intramyocellular lipids. Br J Nutr. 2003;89(03):365–74.
26. Amano Y, Sugiyama M, Lee JS, Kawakubo K, Mori K, Tang AC, *et al*. Glycemic index-based nutritional education improves blood glucose control in Japanese adults: a randomized controlled trial. Diab Care. 2007;30 (7):1874–6.
27. Miller J. The glycaemic index of foods. Asia Pacific J Clin Nutr. 1993;2:107–10.
28. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA. 1997;277(6):472–7.
29. Augustin LSA, Kendall CWC, Jenkins DJA, Willett WC, Astrup A, Barclay AW, *et al*. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). Nutr Metab Cardiovasc Dis. 25(9):795–815.
30. Wolever TM. The glycemic index. World Rev Nutr Diet. 1990;62:120–85.
31. Louie JCY, Brand-Miller JC, Markovic TP, Ross GP, Moses RG. Glycemic index and pregnancy: a systematic literature review. J Nutr Metab. 2011;2010.
32. Brighenti F, Benini L, Del Rio D, Casiraghi C, Pellegrini N, Scazzina F, *et al*. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. Am J Clin Nutr. 2006;83(4):817–22.
33. Jenkins DA, Kendall CC, McKeown-Eyssen G, *et al*. Effect of a low–glycemic index or a high–cereal fiber diet on type 2 diabetes: a randomized trial. JAMA. 2008;300(23):2742–53.
34. Barr S, Reeves S, Sharp K, Jeanes YM. An isocaloric low glycemic index diet improves insulin sensitivity in women with polycystic ovary syndrome. J Acad Nutr Diet. 2013;113(11):1523–31.
35. Wolever TMS, Mehling C. High-carbohydrate low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance. Br J Nutr. 2002;87(5):477–87.
36. Laaksonen DE, Toppinen LK, Juntunen KS, Autio K, Liukkonen K-H, Poutanen KS, *et al*. Dietary carbohydrate modification enhances insulin secretion in persons with the metabolic syndrome. Am J Clin Nutr. 2005;82(6): 1218–27.
37. Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, *et al*. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87(1):114–25.
38. Brand-Miller JC, Holt SH, Pawlak DB, McMillan J. Glycemic index and obesity. Am J Clin Nutr. 2002;76(1):281S–5S.
39. Lavin J, Wittert G, Andrews J, Yeap B, Wishart J, Morris H, *et al*. Interaction of insulin, glucagon-like peptide 1, gastric inhibitory polypeptide, and appetite in response to intraduodenal carbohydrate. Am J Clin Nutr. 1998;68(3):591–8.
40. Holt S, Brand J, Soveny C, Hansky J. Relationship of satiety to postprandial glycaemic, insulin and cholecystokinin responses. Appetite. 1992;18(2):129–41.
41. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics. 1999;103:e26.
42. Wolfe R. Metabolic interactions between glucose and fatty acids in humans. Am J Clin Nutr. 1998;67(3):519S–26S.
43. Pawlak D, Denyer GS, Brand-Miller JC. Long term feeding with high glycemic index starch leads to obesity in mature rats. Proc Nutr Soc Aust. 2000;24:215 (abstract).
44. Zurlo F, Lillioja S, Esposito-Del Puente A, Nyomba BL, Raz I, Saad MF, *et al*. Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. Am J Physiol Endocrinol Metab. 1990;259(5):E650–7.
45. Simoneau J-A, Veerkamp JH, Turcotte LP, Kelley DE. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. FASEB J. 1999;13(14):2051–60.
46. Febbraio MA, Keenan J, Angus DJ, Campbell SE, Garnham AP. Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: effect of the glycemic index. J Appl Physiol. 2000;89(5):1845–51.
47. Kiens B, Richter E. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. Am J Clin Nutr. 1996;63(1):47–53.
48. Howe JC, Rumpler WV, KM. B. Dietary starch composition and level of energy intake alter nutrient oxidation in 'carbohydrate-sensitive' men. J Nutr. 1996;126:2120–9.
49. FAO/WHO. Carbohydrates in Human nutrition: report of a joint FAO/WHO expert consultation. In: FAO/WHO, editor. Rome 14–18 April 1997.
50. Metzler-Zebeli BU, Hooda S, Mosenthin R, Ganzle MG, Zijlstra RT. Bacterial fermentation affects net mineral flux in the large intestine of pigs fed diets with viscous and fermentable nonstarch polysaccharides. J Anim Sci. 88(10):3351–62.

51. Houghton L, Green T, Donovan U, Gibson R, Stephen A, O'Connor D. Association between dietary fiber intake and the folate status of a group of female adolescents. Am J Clin Nutr. 1997;66(6):1414–21.
52. Neish AS, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V, *et al*. Prokaryotic regulation of epithelial responses by inhibition of IjB-a ubiquitination. Science. 2000;289(5484):1560–3.
53. Frost G, Wilding J, Beecham J. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 diabetic patients. Diab Med. 1994;11(4):397–401.
54. Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. Am J Clin Nutr. 2005;81(5):976–82.
55. Frost GS, Brynes AE, Bovill-Taylor C, Dornhorst A. A prospective randomised trial to determine the efficacy of a low glycaemic index diet given in addition to healthy eating and weight loss advice in patients with coronary heart disease. Eur J Clin Nutr. 2004;58(1):121–7.
56. Ghani RA, Shyam S, Arshad F, Wahab NA, Chinna K, Safii NS, *et al*. The influence of fasting insulin level in post-gestational diabetes mellitus women receiving low-glycaemic-index diets. Nutr Diabetes. 2014;4:e107.
57. Wheeler ML, Dunbar SA, Jaacks LM, Karmally W, Mayer-Davis EJ, Wylie-Rosett J, *et al*. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. Diab Care. 2012;35(2):434–45.
58. Rivellese AA, Giacco R, Costabile G. Dietary carbohydrates for diabetics. Curr Atherosclerosis Rep. 2012;14(6): 563–9.
59. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr. 2013;97(3):505–16.
60. Mann JI, Te Morenga L. Diet and diabetes revisited, yet again. Am J Clin Nutr. 2013;97(3):453–4.
61. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, *et al*. Nutrition therapy recommendations for the management of adults with diabetes. Diab Care. 2013;36(11):3821–42.
62. Moses RG, Barker M, Winter M, Petocz P, Brand-Miller JC. Can a low-glycemic index diet reduce the need for insulin in gestational diabetes mellitus? A randomized trial. Diab Care. 2009;32(6):996–1000.
63. Grant SM, Wolever TMS, O'Connor DL, Nisenbaum R, Josse RG. Effect of a low glycaemic index diet on blood glucose in women with gestational hyperglycaemia. Diab Res Clin Pract. 2011;91(1):15–22.
64. Hu Z-G, Tan R-S, Jin D, Li W, Zhou X-Y. A low glycemic index staple diet reduces postprandial glucose values in Asian women with gestational diabetes mellitus. J Investig Med. 2014;62(8):975–9.
65. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. Diab Care. 2014;37(12):3345–55.
66. Moses RG, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, *et al*. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 2006;84(4):807–12.
67. Moses RG, Casey SA, Quinn EG, Cleary JM, Tapsell LC, Milosavljevic M, *et al*. Pregnancy and glycemic index outcomes study: effects of low glycemic index compared with conventional dietary advice on selected pregnancy outcomes. Am J Clin Nutr. 2014;99(3):517–23.
68. Louie JCY, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, *et al*. A randomized controlled trial investigating the effects of a low–glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. Diab Care. 2011;34(11):2341–6.
69. Catalano P, Vargo K, Bernstein I, Amini S. Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. Am J Obstet Gynecol. 1991;165:914–9.
70. Horan MK, McGowan CA, Gibney ER, Donnelly JM, McAuliffe FM. Maternal low glycaemic index diet, fat intake and postprandial glucose influences neonatal adiposity–secondary analysis from the ROLO study. Nutr J. 2014;13(1):1.
71. Durnwald CP, Mele L, Spong CY, Ramin SM, Varner MW, Rouse DJ, *et al*. Glycemic characteristics and neonatal outcomes of women treated for mild gestational diabetes. Obstet Gynecol. 2011;117(4):819.
72. Uvena-Celebrezze J, Fung C, Thomas A, Hoty A, Huston-Presley L, Amini S, *et al*. Relationship of neonatal body composition to maternal glucose control in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2002;12(6):396–401.
73. Pedersen J. Diabetes and pregnancy; blood sugar of newborn infants during fasting and glucose administration. Ugeskrift laeger. 1952;114(21):685.
74. Parker SE, Werler MM, Shaw GM, Anderka M, Yazdy MM. Dietary glycemic index and the risk of birth defects. Am J Epidemiol. 2012;176(12):1110–20.
75. Shyam S, Arshad F, Ghani RA, Wahab NA, Safii N, Nisak MY, *et al*. Low glycaemic index diets improve glucose tolerance and body weight in women with previous history of gestational diabetes: a six months randomized trial. Nutr J. 2013;12(1):1.

76. Östman E, Frid A, Groop L, Björck I. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. Eur J Clin Nutr. 2006;60(3):334–41.
77. Hollenbeck CBCA, Reaven GM. Comparison of plasma glucose and insulin responses to mixed meals of high, intermediate-and low-glycemic potential. Diab Care. 1988;11:323–9.
78. Laine DCTW, Levitt MD, Bantle JP. Comparison of predictive capabilities of diabetic exchange lists and glycemic index of foods. Diab Care. 1987;10(4):387–94.
79. Louie JC-Y, Flood V, Turner N, Everingham C, Gwynn J. Methodology for adding glycemic index values to 24-hour recalls. Nutrition. 2010;30:1–6.
80. Wolever T, Jenkins D, Jenkins A, Josse R. The glycemic index: methodology and clinical implications. Am J Clin Nutr. 1991;54(5):846–54.
81. Wolever T. Relationship between dietary fiber content and composition in foods and the glycemic index. Am J Clin Nutr. 1990;51(1):72–5.
82. Mandel AL, Breslin PAS. High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. J Nutr. 2012;142(5):853–8.
83. Palmer S. Finding a place for the glycemic index. Today's Dietitian [Internet]. 2009;11(6):8 p. Available from http://www.todaysdietitian.com/newarchives/060109p8.shtml.
84. Brand-Miller J, Foster-Powell K, Nutr M. Diets with a low glycemic index: from theory to practice. Nutr Today. 1999;34(2):64–72.
85. Beebe C. Diets with a low glycemic index: not ready for practice yet!! Nutr Today. 1999;34(2):82–6.
86. Sangeetha-Shyam, Fatimah A, Rohana AG, Norasyikin AW, Karuthan C, Nik Shanita S, *et al*. Lowering dietary glycaemic index through nutrition education among Malaysian women with a history of gestational diabetes mellitus. Mal J Nut. 2013;19(1):9–23.
87. Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. Am J Clin Nutr. 2007;86(3):707–13.
88. Shyam S, Arshad F, Ghani RA, Wahab NA, S. NS, Chinna K, *et al*. Effect of including glycaemic index (GI) nutrition education, within the conventional healthy dietary recommendation framework, on body weight and composition of women with prior gestational diabetes mellitus: results from a one-year randomised controlled trial. Mal J Nutr. 2015;21(3):269–83.

Source: Shyam S., Ramadas A. (2018) Treatments with Low Glycaemic Index Diets in Gestational Diabetes. In: Rajendram R., Preedy V., Patel V. (eds) Nutrition and Diet in Maternal Diabetes. Nutrition and Health. Humana Press, Cham. https://doi.org/10.1007/978-3-319-56440-1_19.

In Type 2 Diabetes Uncontrolled on Dual therapy

START EARLY — STEP UP — SYNERGIZE

Glycomet® Trio 1 mg
Metformin HCl 500 mg SR + Glimepiride 1 mg + Voglibose 0.2 mg

Glycomet® Trio 2 mg
Metformin HCl 500 mg SR + Glimepiride 2 mg + Voglibose 0.2 mg

STEP UP

Glycomet® Trio 2 mg/0.3 mg
Metformin HCl 500 mg SR +Glimepiride 2 mg + Voglibose 0.3 mg

In Obese Type 2 Diabetes Uncontrolled on Dual therapy

Glycomet® Trio Forte 2 mg
Metformin HCl 1000 mg SR + Glimepiride 2 mg + Voglibose 0.2 mg

Also Available

Glycomet® Trio Forte 1 mg
Metformin HCl 1000 mg SR + Glimepiride 1 mg + Voglibose 0.2 mg

Glycomet® Trio 1 mg/0.3 mg
Metformin HCl 500 mg SR + Glimepiride 1 mg + Voglibose 0.3 mg

For the use of a Registered Medical Practitioner, Hospital or Laboratory only.