Chapter 1

Diabetes Mellitus in South Asia

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Additional information is available at the end of the chapter

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Abstract

The prevalence rates of diabetes mellitus and its complications in South Asia are much higher than in other developed and developing countries; therefore, diabetes mellitus has become a serious problem in this region. While the prevalence of diabetes mellitus in South Asia is remarkable, its characteristics and causes have not been well-elucidated. More than 85% of the diabetic population in South Asia suffer from type 2 diabetes, and the causes can be divided into two categories: internal/traditional causes and causes induced by rapid development. Factors such as age, gender, diet and lifestyle changes, including a lack of physical activity caused by modernization and urbanization, are major contributory factors. The majority of the healthcare costs associated with diabetes are due to its later complications and are not preventable. Therefore, inexpensive treatment at an early stage of diabetes is important. In this review, the following are recommended as preventive measures of the incidence of the disease: (1) induction of UCP1 through the diet, (2) increasing the intake of antidiabetic bioactive components and/or food and (3) evolution of the consensus through educational programs and government policy. National strategies and interventions should be implemented immediately for both the primary and secondary prevention of diabetes mellitus and its complications in order to advocate healthy living among the South Asian populations.

Keywords: diabetes mellitus, diabetic complications, India, South Asia, Sri Lanka

1. Introduction

Diabetes mellitus (hereafter referred to as "diabetes") develops under unusual conditions where the glucose level in the blood cannot be controlled. The disease is characterized by several symptoms such as thirst, polyuria and blurred vision [1]. Ketoacidosis or a nonketotic-hyperosmolar state caused by a chronic higher blood glucose level leads to stupor and coma in advanced cases and can even cause death in severe cases. There are four clinically defined

categories of diabetes: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM) and other specific types of the disease [2, 3]. In T1DM, also known as insulin-dependent diabetes (IDDM), the body is unable to produce insulin because of the autoimmune destruction of pancreatic islet beta cells (β cells), and as a result, the glucose levels in the blood cannot be maintained at normal concentrations. It ranks as the most common chronic childhood disease. T2DM or noninsulin-dependent diabetes (NIDDM) is characterized by both impaired insulin secretion and impaired insulin action. This type is associated with aging, obesity, a family history of diabetes, physical inactivity and certain ethnicities, although the causes of some of these factors are not well-explored. In GDM, the most widely accepted definition is diabetes that develops by varying insulin sensitivity during pregnancy or diabetes first recognized during pregnancy; in the former case, treatment with insulin can often be finished after pregnancy, as this type of diabetes is acute. Among these categories, T2DM accounts for about 85–95% of diabetes cases worldwide.

Diabetes research has mainly focused on people living in developed countries as a disease caused by obesity. However, the prevalence rate of diabetes has been increasing in many developing and newly-industrialized nations as well. In this review, we focused on South Asia as one such region. The prevalence rate of diabetes and its complications in South Asia is higher than in other areas, such as Europe [4], and diabetes has recently become a serious health issue leading to death [5]. Therefore, comprehensive knowledge about the prevalence rate and causes of diabetes in South Asian countries is desired. As part of this review, we investigated the present state, characteristics and causes of diabetes in South Asia and proposed strategies for its prevention. We hope that this appraisal will encourage recognition of the serious state of diabetes among South Asians and become an effective index for eventually solving this issue.

2. An overview of the prevalence of diabetes in South Asians

South Asia comprises the Indian subcontinent and is home to a diverse population of ethnic, linguistic and religious groups. The total population of South Asia is about 1.5 billion, representing more than 20% of the global population. The countries that fall under this regional demarcation include India, Pakistan, Sri Lanka, Nepal, Bhutan, Maldives, Afghanistan and Bangladesh. With deviating definitions based on often substantially different reasons (usually political), the British Indian Ocean Territory, Mauritius, Iran and the Tibet Autonomous Region are sometimes included as part of the South Asian subcontinent as well. Nevertheless, for the purpose of this review, we defined South Asia as India, Pakistan, Sri Lanka, Nepal, Bhutan, Maldives, Afghanistan and Bangladesh and focused on the diabetes status of the people living in these countries.

A recent study using a Diabetes Population Risk Tool in Canada showed that South Asians have the highest risk of developing diabetes [6], and another study estimated that the prevalence rate of diabetes in South Asians was around four times higher than in other ethnic groups [7]. The total number of people with diabetes in the world is estimated to increase from 171 million in 2000 to 366 million by 2030 [8]; this number among South Asians is predicted to reach 46 million in India, 14 million in Pakistan and 11.1 million in Bangladesh by 2030 [9].

A huge number of people (3.8 million) annually lose their lives due to diabetic complications, a value almost equivalent to the loss of life associated with AIDS [7]. **Table 1** shows the diabetic populations and its prevalence rates in South Asian countries based on the data of the International Diabetes Federation, which was estimated by a statistical investigation of the relevant populations primarily 20–79 years of age [10]. The results suggest that the diabetic populations and the prevalence rates of diabetes in most South Asian countries are thus expected to dramatically increase at a high rate until 2035. In India in particular, which has a large population and is rapidly advancing economically, 109 million people are predicted to develop diabetes by 2035 (**Table 1**). This will place India at the epicenter of this global epidemic [11]. In addition to this upward trend in the prevalence rate, the number of deaths and the economic burden due to diabetes in South Asians have been rapidly increasing. As shown in **Table 1**, around 43–870 USD per person is paid to cure diabetes and its complications. With the rising rate of incidence, people in South Asia will have to compensate for much higher diabetes-related expenditures in the near future, which will constitute a heavy burden upon the respective countries [12, 13].

Countries	A (in 1000s)	B (%)	C	D (USD)	E (in 1000s)	F (%)
Afghanistan	13086.9	6.15	18,514	102	27768.7	6.63
Bangladesh	94378.5	6.34	111,371	43	133493.5	8.18
Bhutan	474.0	4.94	124	150	656.9	6.90
India	774920.8	8.63	1,039,980	95	1042007.9	10.46
Maldives	214.0	7.97	109	870	332.9	5.94
Nepal	15307.4	4.58	14,778	60	23032.1	5.44
Pakistan	102124.6	6.80	87,548	56	158355.1	8.08
Sri Lanka	14155.4	8.32	16,384	123	16398.4	9.47

A, total adult population (20–79 years) in 2014; B, diabetes prevalence per total adult population in 2014; C, deaths number by the disease related to diabetes in 2014; D, mean diabetes-related expenditure per person in 2014; E, estimation of total adult population in 2035; F, diabetes prevalence per total adult population in 2035.

Table 1. Prevalence of diabetes in South Asia in 2014 and its estimated prevalence in 2035.

3. High prevalence rates of complications related to diabetes in South Asians

3.1. Prevalence rate of macrovascular complication

Diabetes is known to be strongly associated with many other disease and complications, and those ultimately lead to organ and tissue damage. The prevalence rates of macrovascular complications and atherosclerosis are especially high in diabetic patients, inducing adverse effects of ischemic heart disease [14], peripheral vascular disease and cerebrovascular disease. Diabetes is suspected to induce macrovascular complications and atherosclerosis. High blood

glucose and insulin concentrations in diabetic patients induce structural and functional alterations and chronic inflammation at the arterial cell walls. Macrophages gather and invade the inflammation portion, forming plaque. This advanced plaque buildup is known as atherosclerosis. The main disease leading to death in diabetic patients is cardiovascular disease, with cerebrovascular disease and diabetic stroke being the second and third highest causes of death. The ratio of stroke in diabetic patients is two- to fourfold higher than in nondiabetic patients, and diabetics show a greater possibility of recurrence of stroke [15]. Furthermore, peripheral arterial disease (PAD), which is characterized by the occlusion of the arteries in the limb region and results in functional impairment and disability with intermittent claudication and pain, is also closely related to diabetes [15]. In most unfortunate cases, PAD causes foot ulceration, ultimately requiring amputation [16]. It is known that diabetic patients have a 25-times-greater risk of amputation than nondiabetes population.

It has been reported that Asian patients with diabetes are at a higher risk of developing macrovascular complications, such as cardiovascular disease, than other ethnicities [17]. For instance, a study conducted in Pakistan revealed that 30.5% of the young adult patients diagnosed with ischemic stroke were diabetic—a much higher percentage than in Western settings [18]. Another study performed in ischemic stroke patients of <45 years of age in Sri Lanka revealed that 5% of the study group with ischemic stroke had diabetes [19]. A prospective study was also conducted in 2403 patients with ischemic stroke and 783 patients with intracerebral hemorrhaging in India as a representative South Asian country [20]. That report mentioned that Asian diabetic patients had a high risk of early death due to ischemic stroke [20]. Furthermore, reports on the risks of cardiovascular disease and coronary in the Indian subcontinent have suggested that a leading cause of those diseases was diabetes [21, 22].

3.2. Prevalence rates of diabetic retinopathy, nephropathy and neuropathy

Another serious complication in diabetic patients is dysfunction of the eyes, kidneys and nerves. Diabetic retinopathy, a typical peripheral microvascular complication, induces acute damage to the retina of the eye [23]. Diabetic retinopathy is divided into two categories: background and proliferative retinopathy [22]. In background retinopathy, slight hemorrhaging develops in the middle layers of the retina, appearing as dots. In proliferative retinopathy, the formation of new blood vessels occurs on the surface of the retina, and white areas on the retina are a sign of this type of disease. Several studies have shown that the occurrence of diabetes retinopathy is influenced by chronic insulin resistance and a high blood glucose concentration, which occur in obese patients [24]. A poorly controlled blood-sugar level is the most significant factor associated with the development of retinopathy. The prevalence rate of retinopathy in diabetic patients in South Asia has been explored in several studies. One study investigated the rate in patients newly diagnosed with diabetes in India and found that the rate was lower (5–7%) than in both Western countries and neighboring countries such as Pakistan (15%), Nepal (19.3%) and Sri Lanka (15%) [25]. However, a similar study conducted in an urban population in Chennai, India, revealed that the prevalence of diabetic retinopathy per diabetic patient was 18%, although the prevalence of diabetic retinopathy in the general population was only 3.5%. Furthermore, men were shown to be at a higher risk than women in that investigation [26].

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Diabetes nephropathy is also a serious complication. High blood pressure induced by both atherosclerosis and the function of adipose tissue causes the dysfunction of renal tissue. In the early stages, albumin in the urine is excreted at 30–299 mg per 24 h, which is called "microalbuminuria" and leads to renal failure at the final stage. A study found that one-quarter of patients with T1DM suffers from microalbuminuria or its advanced stage, diabetes nephropathy [15]. Some studies have reported on the prevalence rate of diabetic nephropathy in South Asians [27]. A study conducted in 10 countries in Asia, including Pakistan, found that the ratio of patients developing microalbuminuria per diabetic patient was alarmingly high (58.6%) [28]. A similar study conducted in an urban setting in South India revealed that the prevalence rate of microalbuminuria per diabetic patients was 26.3%, although the prevalence rate of overt nephropathy was only 2.2% in the study subjects [29]. These studies suggested that duration of the diabetes and hypertension is highly correlated with the development of nephropathy in South Asians.

Microalbuminuria caused by diabetes also induces peripheral nerve dysfunction, and half of diabetic patients consequently develop diabetic neuropathy [15]. The American Diabetic Association has stated that diabetic neuropathy is a sign of peripheral nerve dysfunction [30]. Among the symptoms of diabetic neuropathy, autonomic neuropathy is the most common. This symptom leads to an abnormal heart rate, loss of vascular control and cardiovascular autonomic dysfunction. Cardiac neuropathy caused by diabetes is the second-most common manifestation, depending on age, hypertension, smoking status and obesity. The prevalence rate of diabetic neuropathy in South Asia has been investigated. A study conducted in Sri Lanka reported that the prevalence rate of distal peripheral neuropathy (DPN) among T2DM patients was 24% (females and males: 26% and 20%, respectively). The prevalence rate of neuropathy among T2DM patients in South India was 19.1%, and this number is gradually increasing [31]. A similar study conducted in Indian states reported that the prevalence rate of diabetic neuropathy was 26.1% and was significantly associated with age, glycated hemoglobin and duration of diabetes [30]. Overall, **Figure 1** shows a schematic illustration of the

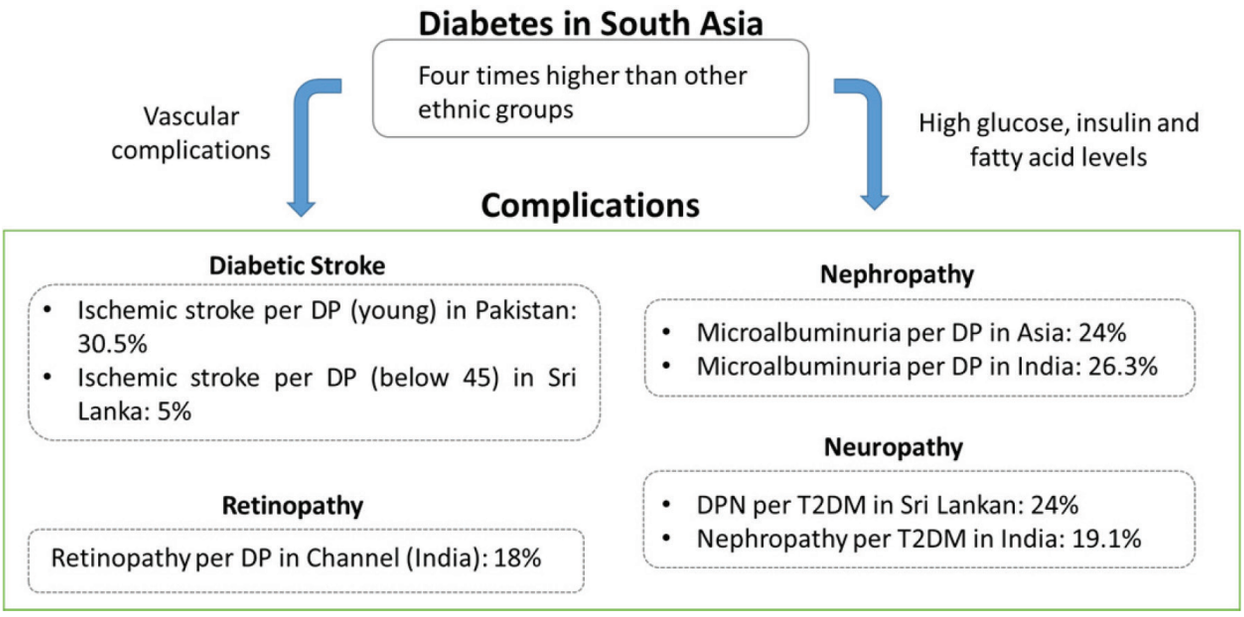

Figure 1. Prevalence rates of diabetes and its complications in South Asia (DP: diabetic patients).

typical course of diabetes and its complications in South Asia, as explained in this section. It is evident that the prevalence rates of diabetes and its complications in South Asians are much higher than in other countries. Therefore, recognition of this critical situation is duly warranted in order to mitigate the propagation of the disease condition.

4. Causes of the high prevalence rate of diabetes in South Asians

4.1. Physiological and traditional causes

4.1.1. Genetic factors

In this section, we explore why the prevalence rate of diabetes in South Asia is so much higher than in other developed or developing countries. Among the causes, genetic factors seem to be important, as a study suggested that 30–70% of the diabetes risk could be attributed to genetic variants (SNPs of diabetic genes) [32]. Genetic variants causing diabetes have been screened since the 1990s [33]. Around 50 genetic variants, known as "obese genes" or "thrifty genes" have been identified, and the relationship between diabetes and genetic variants of β3-adrenalin receptor—a thrifty gene—have been examined in particular detail. Individuals with a variant genotype of a thrifty gene proactively store fat in the body by reducing the energy metabolism; this is beneficial in times of nutrient scarcity [34, 35]. Asian populations are much more likely to possess thrifty genotypes than Europeans. The reason for this is believed to be because South Asian populations have not had sufficient time to adapt from this variant genotype to a normal genotype, as Europeans evolved in environments where they were relatively unaffected by famine cycles [32].

Several studies have reported that South Asians have several risk factors for disorder of glucose consumption and insulin resistance. For instance, features of insulin resistance, such as hypertriglyceridemia, and increased abdominal or visceral fat have been seen even in nonobese Asian populations [36–38], and South Asians have more adiposity than Europeans and residents of other parts of the world with the same body weight [39, 40]. Furthermore, South Asians are more insulin resistant than other races [36, 41]. Studies conducted in India as representative South Asians have reported that Indians were at a higher risk of glucose intolerance than Europeans, even in groups with a low waist circumference [42, 43]. Insulin resistance and compensatory hyperinsulinemia have been found even in children and adolescents of Asian-Indian origin [44]. These studies firmly suggest that South Asians have a special variant genotype of the thrifty gene strongly inducing insulin resistance and unusual glucose consumption. The Asian Indian phenotype—a thrifty gene seen among Pima Indians, is the most likely candidate for this special variant among the recognized thrifty genes based on the findings from several studies [36, 37]. Studies have shown that migrant Asian-Indians had a higher risk of developing diabetes and related metabolic abnormalities than other ethnic groups [37] and that the prevalence rate of diabetes and its adverse health effects has risen more rapidly among native and migrant populations in South Asia than in any other geographic region. However, another study that included 20,119 participants from

South Asia revealed a considerable degree of genetic contribution to the onset of T2DM [45]. The researchers identified novel six loci (GRB14, ST6GAL1, VPS26A, HMG20A, AP3S2 and HNF4A) showing correlations with T2DM [45]. Therefore, the diabetic constitution in South Asia is suspected to be related to other genes in addition to the Asian Indian phenotype.

4.1.2. Effects of family history, age and gender

Individuals' profiles are important to consider when examining the prevalence rate of diabetes [46]. The incidence of the disease in a patient's family is often involved in a given individual's risk, as the variant genotype of thrifty genes is passed down from parents to offspring. Studies comparing the effect of family with others estimated that the risk factors for diabetes in offspring with a single diabetic parent and two diabetic parents are, respectively, 3.5- and 6-fold higher than those without parental diabetes [47]. Among patterns of inheritance, diabetes and its related traits are both polygenic and heterogeneous, with multiple genes involved in different combinations [48]. However, the number of risk genes and their relative contributions are complicated and remain somewhat uncertain. A relationship is known to exist between diabetes and age, probably because the β-cells of older individuals have a reduced proliferative capacity and secreting activity, reduced expression of cell cycle activators, increased expression of cell cycle inhibitors, reduced pdx1 expression and increased amylin aggregation [49]. This decreased functional status is exacerbated in diabetic patients by increased rates of beta cell apoptosis [38]. In addition, in South Asia, elderly people tend to have a decreased muscle mass due to sedentary lifestyles [17].

In South Asians, diabetes does not always develop in the elderly, and the characteristics are remarkable. An investigation on the prevalence rate of diabetes in various age groups of South Asians showed that the diabetes population was highest among those ≥60 years of age for both males and females. However, the rate of diabetes among relatively young individuals was found to be higher in South Asians than Caucasians [37]. Furthermore, in India, the prevalence rate of diabetes peaks at 60–69 years of age [42], and Indian people develop the disease even in their youth [41]. Similar results to those in India were found in Pakistan and Sri Lanka [47]. The development of diabetes in younger generations is likely caused by changes in lifestyle brought about by urbanization [42]. The prevalence rate of diabetes (5.02%) was found to be associated with age-adjusted impaired glucose intolerance (5.27%) in a rural community in Sri Lanka [47]. Diabetes develops at any age, and the change in the prevalence over time is hypothesized to be associated with the rural to urban population shift [49].

The prevalence rate is also related to gender in South Asia. Diabetes is the second leading cause of death among South Asian women with diabetes, although it is only the ninth leading cause globally [9]. A relationship was reported between age and gender in Bangladesh diabetes patients [50]. The proportion of female diabetic patients (31.2%) was higher than that of male diabetic patients (28.5%) among subjects 31–50 years of age. Among subjects >50 years of age, the diabetic male population was 18.1% and that of the female population was 12.9%. However, below 31 years of age, only 3.3% of the male population had diabetes, whereas 6% of the female population was diabetic [51]. A study conducted in four provinces of Sri Lanka showed that the prevalence of severe obesity among males was 2.4%, whereas that among

females was 8.8%. Further, the report found that, in all categories of overweight, the prevalence was greater in women than in men in all provinces [50]. Women with diabetes are also more likely to suffer a heart attack at a younger age than those without diabetes.

Gestational diabetes may be the main reason why there is a high prevalence rate of diabetes in women in South Asia, because the prevalence rate of GDM in South Asia is much higher than that in Europe [52, 53]. One cause of the high prevalence rate in South Asia is considered to be genetic factors. Several studies have suggested that South Asians basically have a constitution that is conducive to the development of GDM [53, 54]. Another cause is the influence of sociocultural and socioeconomic factors [55]. Weight and physical activity should be carefully controlled in order not to develop GDM before and during pregnancy. However, actions based on incorrect knowledge and bad traditional habits for pregnancy, which are taught from a person's mother, can lead to an increase in weight and a decrease in physical stress [55]. To make matters worse, GDM often causes miscarriages or birth defects, and the children born from mothers developing GDM also have a tendency to develop diabetes. Therefore, the prevention of GDM is very important to stop the passing of diabetes from mother to children and to decrease the development of diabetes among women in South Asia. It is hoped that future studies on diabetes in South Asia will focus on gestational and neonatal diabetes, and programs to prevent GDM should be established in the field at all governmental levels.

4.1.3. Chronic and heavy intakes of alcohol and smoking

Chronic drinking of large amounts of alcohol exacerbates a potential risk factor of diabetes [50]. The liver is an important organ for consuming and supplying glucose. As the chronic intake of high concentrations of ethanol induces alcoholic liver injury and inhibits the capacity to control the blood glucose level, the liver accumulates triglycerides. Such a liver condition is known as "alcoholic fatty liver." The serum levels of acetaldehyde, an intermediate metabolite of ethanol, are increased by the decrease in the detoxification capacity under conditions of alcoholic fatty liver, often severely adversely affecting the β-cells in the pancreas. Dysfunction of the liver and β-cells causes hyperglycemia, dyslipidemia and diabetes. In all South Asian countries, chronic and heavy drinking is traditionally common in poor rural regions; in addition, alcohol consumption is on the rise with rapid globalization and socioeconomic development. For instance, alcohol use among Indians has been increasing because the lifestyle patterns have been rapidly changing due to migration to urban regions and socioeconomic changes [56]. Public health policies regarding alcohol consumption are needed to stem this tide of change.

Cigarette smoking is an indirect but important risk factor for diabetes [57]. Studies have reported that a smoking habit increased the risk of developing diabetes by 44% [58], and smokers are 30–40% more likely to develop diabetes than nonsmokers [59]. Several studies have attempted to elucidate the relationship. Smoking reduces the insulin sensitivity because nicotine included in cigarettes has the ability to inhibit insulin secretion via neuronal nicotinic acetylcholine receptors. Furthermore, smoking damages cells by increasing the amount of reactive oxygen [60], and inflammation occurs at the damaged portion, causing swelling of cells. Smoking is also associated with an increased risk of abdominal obesity [39]. These harmful effects cause metabolic disorders of glucose and lipids and increase the risk of diabetes as

a result. The percentage of regular smokers in adult males of South Asia is estimated to be very high (50–60%). India is the second-largest producer and consumer of tobacco products. Many persons in India use smokeless tobacco products such as betel quid, as these are non-taxable, and those products are commonly used in rural areas of the country [58]. Concurrent use of alcohol and tobacco, which is also extremely common among South Asian populations, has a synergistic effect on the enhancement of diabetes risk [56]. With the spread of chewing tobacco, smoking is being taken up by younger and younger individuals. An investigation in 7735 British men of 40–59 years of age suggested that the consumption of tobacco, either as a smoker or user of chewing tobacco, is occurring at lower ages, and 47% of men and 14% of women who admitted to consuming tobacco had started at age 15 [57]. Reducing heavy smoking rates and the concurrent intake of alcohol are important targets for preventing diabetes and its complications among South Asians [59]. Changes in the policy and effective education programs for tobacco use in addition to alcohol use must be implemented as soon as possible.

4.2. Causal factors of diabetes induced by rapid globalization and development

4.2.1. Urbanization

Unprecedented urbanization of rural areas of South Asia is a major environmental factor involved in the increasing rate of diabetes [61]. **Table 2** shows the ratio of urban/rural localization among diabetics based on data from the International Diabetes Federation. The urban prevalence of diabetes in Sri Lanka is lower than that in rural areas [5], and similar incidences can be seen in India, Pakistan, Nepal and Afghanistan. In contrast, in countries such as Bangladesh, Bhutan and the Maldives, where urbanization has not rapidly occurred, an opposite trend is shown [5]. This is a characteristic of importance, as the prevalence rate of diabetes is generally high in urban areas (12.4%) followed by the midland (8.1%), highland (5.8%) and coastal areas (2.5%) in developing countries. To further highlight this anomaly, in Japan—which is a developed country—the prevalence rate in urban areas is similar to that in rural areas.

	Effects of gender on diabetes*		**Effects of area on diabetes****	
Countries	**Female (in 1000s)**	**Female/male (–)**	**Urban (in 1000s)**	**Urban/rural (–)**
Afghanistan	407.00	1.02	228.59	0.40
Bangladesh	3261.80	1.20	3053.02	1.50
Bhutan	9.60	0.69	12.11	1.17
India	31384.00	0.88	30571.31	0.89
Maldives	8.00	0.88	4.75	1.51
Nepal	196.40	0.38	244.02	0.57
Pakistan	3369.70	0.94	2934.76	0.78
Sri Lanka	569.60	0.94	330.11	0.41

* Data from Diabetes Atlas in 2014.

** Data from Diabetes Atlas in 2013.

Table 2. Ratio of diabetes by gender and area of South Asia.

Rapid urbanization gives important variation of rural area where agriculture had been the principle profession [9]. Urbanization has reduced the physical activity and altered dietary habits by changing the lifestyle among residents of rural areas through means such as increased mechanization of the agriculture industry, automation of daily activities, popularization of television and increased computer usage, which has accordingly increased the proportion of obese persons [9, 10]. Studies have shown that the prevalence rate of diabetic complications is associated with wealth/income, education and office-based occupations in South Asia [62]. Socially deprived urban South Asian communities have a lower prevalence of diabetes and obesity than developed countries [1], and a study performed in Sri Lanka reported that the majority of patients developing diabetic neuropathy resided in rural areas (75.3%) with a monthly income exceeding Sri Lankan Rs. 12,000 (87.6%) [31]. The inhabitants of South Asian countries who reside in rural areas and show a low prevalence of diabetes are involved in agriculture and engage in intense physical labor. These results suggest that the affluence accompanying urbanization leads to a luxurious—and by extension—more sedentary lifestyle, thereby increasing the rate of diabetes [63].

4.2.2. Increase in the rate of obesity due to changes in the diet

Obesity is a major determinant of T2DM. Many recent studies elucidated the mechanism underlying the development in T2DM. White adipocytes secrete adipokines, such as leptin, adiponectin and TNF-α. Leptin and adiponectin enhance the capacity of glucose consumption by increasing the noradrenalin secretion, but TNF-α inhibits it via the inhibition of insulin receptor and transport of GLUT4 [64]. As the secretion of leptin and adiponectin is decreased and the secretion of TNF-α is increased in white adipose tissues highly accumulating triglyceride, the glucose intake is inhibited [65]. Furthermore, the pressure on blood vessels induced by hypertrophic white adipose tissues causes an inflammatory response, and the enhanced concentration of free fatty acids in the blood by obesity causes the dysfunction of mitochondria in muscle cells and β-cells of the pancreas [66, 67]. These harmful effects induce disorder of glucose consumption and insulin resistance, thereby resulting in the development of T2DM.

Urbanization in South Asia is a major contributory factor to obesity [68, 69]. Investigations conducted among rural communities in Sri Lanka showed a strong relationship between diabetes and excess body weight, and the prevalence rate of obesity in diabetic patients (21%) was higher ($P < 0.05$) than in nondiabetic individuals (10.5%) [70]. Obesity is no longer a disease of affluent and therefore majority of the populations in South Asia in the wake of rapid changes in lifestyle among more rural populations [58]. As previously stated, migration toward rural areas of South Asia induced dramatic changes to the diet within a decade. Traditional dietary patterns are now being lost, and a significant transition to energy-rich diets is occurring in South Asia. The diet has shifted from relatively monotonous food products like indigenous staple grains or starchy roots, locally grown legumes, other vegetables and fruits, along with limited foods of animal origin (except for prosperous subpopulations), to more varied diets that include more preprocessed foods with higher fat and lower carbohydrate content, more foods of animal origin, edible oils and more added sugars, especially in the form of processed drinks and foods, and often more alcohol. These changes in diet have caused a rapid increase in the obese population of South Asia.

The amounts of fats and carbohydrates as well as the total calories strongly influence the rate of obesity, and the body mass index (BMI), glycemic index (GI) and glycemic load (GL) can be used as indices to estimate the amounts of fats and carbohydrate. Many nations in South Asia tend to have relatively high-GI and high-GL diets. For example, white rice, which is a daily staple of the South Asian diet, has a higher GI than whole-grain rice. A recent meta-analysis found that a single increment in white rice serving per day increased the risk of diabetes by 11% [71]. Furthermore, large portion sizes and predominantly starch-based diets in South Asians, which correspond to a high GL, are also associated with obesity. Reducing the carbohydrate portion sizes and increasing the portion of vegetables is necessary to reduce the diabetes risk, as high-GI and high-GL diets contribute to obesity [71, 72].

4.2.3. Increase in undesirable lifestyles and a shortage of education programs

Poor lifestyles, such as a short sleeping time, watching TV for a prolonged period and physical inactivity brought about by urbanization, may function as factors exacerbating and triggering the development of diabetes. The sleep duration among Asians is relatively short. In a meta-analysis of data from 23 countries, adolescents in Asia were sleeping 40–60 min less each night than Americans and 60–120 min less each night than Europeans [73]. Some studies have suggested that this short duration of sleep in Asians was associated with an increased risk of diabetes, childhood obesity and cardiometabolic abnormalities [73, 74]. As sleep-disordered breathing induces a twofold increase in the risk of diabetes [73], a short duration of sleep may induce a condition similar to that of sleep-disordered breathing.

Inactive behaviors (watching TV or playing on a PC for a prolonged period and sedentary careers) may also be associated with diabetes in South Asians. Prolonged stints of watching TV are independent of the metabolic activity for obesity, but wasting so much time with this behavior tends to be associated with an unhealthy diet, including increased consumption of snacks, sugary beverages and fast food [38]. Furthermore, this lifestyle is associated with physical inactivity due to a decrease in the metabolic capacity when performing such daily work. Therefore, watching TV for a prolonged period consequently increases the prevalence rate of obesity and diabetes. In addition, many studies in South Asians have revealed a rapid shift to careers in the service sector due to economic growth and the advent of new technologies. This has led to careers involving long durations of sitting, thereby resulting in a marked decline in physical activity [38]. People in a high socioeconomic class are more prone to developing diabetes than those in lower economic classes. Of special note, a study in adults in Sri Lanka revealed a strong association between physical inactivity and diabetes [75].

Education about diabetes is much more lacking among South Asians than in Europeans, and this low consciousness of diabetes has consequently contributed to an increase in the rate of diabetes in South Asians. A study conducted in Bangladesh found that individuals with more education had a 1.67-fold lower risk of developing diabetes than those with little or no education [75]. In that study, employees who had often been educated about diabetes had a lower probability of having diabetes themselves than unemployed individuals [75]. Another study in Sri Lankans showed that a higher educational level may be associated with better diabetes-related outcomes [70]. Therefore, education starting from elementary school may be an effective and practical

way of reducing the rate of diabetes. The World Diabetes Foundation has already implemented prevention programs at the national level to educate students in urban and semi-urban areas in South Asian countries about the risk of diabetes, in view of these shortcomings [76].

Figure 2 shows a schematic illustration of the characteristics of diabetes in South Asia described in this chapter. The causes underlying the high prevalence of diabetes in South Asians can be distilled down to four main factors. First, South Asians have the thrifty gene derived from Asian Indian populations that induces insulin resistance and disorder of glucose consumption; they therefore develop a T2DM constitution. Second, obese populations are increasing due to dietary changes and a decrease in physical activity in the wake of remarkable economic progress, which causes T2DM. Third, traditional bad habits such as chronic heavy smoking and drinking, which cause T1DM and T2DM, are increasingly being adopted due to increased income caused by economic progress. Fourth, the recognition to diabetes is poor because of a lack of relevant policies and the education system.

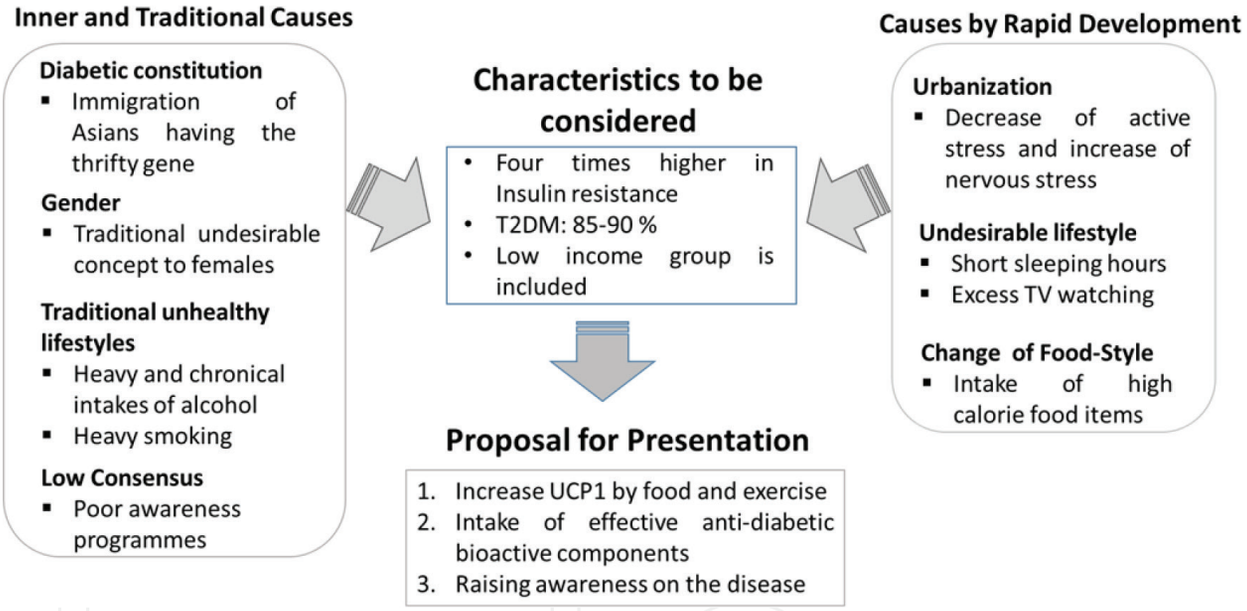

Figure 2. Causes of diabetes in South Asia and suggestions for their prevention.

5. Strategies for preventing diabetes in South Asia

As we suggested in the previous sections, the implementation of preventive strategies for diabetes is necessary as soon as possible. Preventive treatment should be performed as early as possible in subjects at risk of developing diabetes, as complete recovery is extremely difficult once diabetes develops. Second, the recovery of the glucose consumption capacity and insulin sensitivity are the most important targets for treatment because most diabetic patients in South Asia have T2DM, which is mainly caused by disorders in these activities. Furthermore, inexpensive treatments are necessary, as diabetic patients in South Asians tend not to be very wealthy. Given these aspects, we propose three strategies herein for reducing the prevalence

rate of diabetes. The first strategy involves the induction of uncoupling protein 1 (UCP1) by changing the diet and lifestyle. UCP1, which is expressed only in brown adipocytes, plays a role in nonshivering heat generation using the proton potential of the inner membrane of mitochondria. Through the effects of UCP1, fatty acid is effectively metabolized to compensate for the loss of energy. Recently, the effects of UCP1 on glucose and insulin resistance were examined using fatty mouse and UCP1 transgenic mouse models [77–79]. The results of those studies suggest that increasing the concentration of UCP1 is the most effective way to rescue subjects with preliminary T2DM. The induction of UCP1 is relatively easy because muscle cells and white adipocytes can be differentiated to brown adipocyte by the stimulation of cool temperatures and exercise [80, 81] or by consuming herbal and/or complementary medicines [66]. We therefore think that the induction of brown adipocytes is the most inexpensive and effective way of preventing the development of diabetes at the early stage in South Asia.

The second strategy involves qualitative improvements in the diet by proactively consuming functional compounds or food products containing antidiabetic bioactives. Many effective compounds for protecting against obesity have been identified. For example, consuming fish instead of meat is good for protecting against obesity because DHA contained in fish can reduce fat and cholesterol. Proactively consuming food containing polyphenols, such as green tea, soybean products and berries, and carnitine, such as fish [82–84], is also effective for similar reasons. Superfoods that contain high levels of these effective compounds and functional foods with artificially enhanced levels have been enthusiastically studied, and many inexpensive functional foods and supplements are now available in developed countries [85, 86]. The proactive consumption of superfoods and functional foods through the daily diet without expensive drugs is extremely effective for protecting against obesity and diabetes.

The final and most important strategy involves changing the consensus. If most South Asians with obese constitutions continue their bad habits, such as chronic heavy smoking and drinking and consuming high-calorie and oily foods, the rapid increase in the prevalence rate of diabetes cannot be effectively curbed. In Japan, the consensus regarding obesity and metabolic syndrome has recently been enhanced by a trend toward anti-obesity and education via TV and books; in this way, the rising tide of obesity is being stemmed little by little. This is a strategy which could be easily implemented in South Asia as well. Therefore, revising the consensus can be effective, even in South Asians. In a case report from Ballabgarh, India, a five-step model (identify the problem, understand the problem, evaluate feasible and cost-effective intervention) is addressed to the issue [87], but statistics clearly display that such efforts are not sufficient, and further education toward diabetes and national strategies and interventions to protect against obesity and diabetes should be implemented immediately.

6. Conclusion

We focused on the issue of the recent increase in the diabetes prevalence in South Asia and described the results consequently obtained in associated studies. First, we investigated the prevalence of diabetes and its complications in South Asia. Existing studies and statistics suggest that the prevalence was much higher in this region than in other developed and developing countries

and that this prevalence is rapidly increasing despite already being a serious problem in the subcontinent. This high prevalence rate will induce increased diabetes-related expenditures and incur a heavy financial and social burden in the near future for people in South Asia.

Second, we examined why South Asians show a higher prevalence rate of diabetes than other populations and explored the reasons for its rapid increase in prevalence. One potential internal cause is a constitution based on obesity, which is induced by the thrifty gene characteristic of Asians. Another potential internal cause is the adoption of traditional bad habits, such as chronic heavy smoking and drinking. These factors may cause T2DM even in nonobese subjects and T1DM even in older individuals. A potential environmental cause is urbanization. Rapid development gives rise to an undesirable diet and lifestyle, which can cause obesity in South Asians, especially those living in rural areas.

Finally, we proposed effective prevention strategies based on the above analyses. Primary prevention through the promotion of a healthy diet and lifestyle should be a priority, and the prevalence rate may be able to be drastically decreased by making changes to one's diet and lifestyle. However, if South Asians fail to recognize the impending diabetes crisis, this condition will unfortunately become much more serious in the near future. The implementation of public health strategies aimed at mitigating the obesogenic environment is critical.

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