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Recent Advances Input for Better Management Practices of Diabetes Mellitus Type II

Dr. Suresh Kishanrao*

Family Physician & Public Health Consultant, Bengaluru, Karnataka, India.

***Corresponding author:** Dr. Suresh Kishanrao, Family Physician & Public Health Consultant, Bengaluru, Karnataka, India.

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Abstract

Diabetes research, diagnosis and management in developing world including India face challenges of limited resources, access to healthcare, low awareness, financial burdens, and adherence issues which are more pronounced in rural areas & among certain socioeconomic groups, cultural & dietary influences. Physicians' limited time and knowledge and lack of efforts to update themselves also play a role.

Most people in middle- and low-income countries know that Type 2 diabetes is strongly linked to unhealthy lifestyles, including poor diet, lack of physical activity, and obesity apart from the risk factors of Ethnicity, age, family history, & genetic factors. They also know that uncontrolled blood sugar levels lead to serious health complications, like heart disease, stroke, kidney disease, nerve damage, and vision loss.

But research across the world mostly in developed countries are sharing that there are other linkages which influence diabetes diagnosis and management, which very few people and even Primary health care providers know and consider in changing treatment practices. These include i) onset diabetes, ii) Menstruation link to underdiagnosis, iii) linkages between Sleep Deprivation iv) diabetes in elderly and Aging syndrome, v) Type 5 diabetes, vi) Environmental pollution with PM 2.5 Pollution, viii) Vitamin D deficiency, & ix) Age-specific body weight.

Materials and Methods: *This article is an outcome of seeing one case each of onset of diabetes in lady aged 62 years, use of CGM showing intraday variations in Blood sugar levels, multiple cases of diabetes among elderly and appropriate literature search on recent advances in issues influencing diabetes management apart from the well-known factors like unhealthy lifestyles, lack of physical activity, obesity, ethnicity, age, family history, & genetic factors.*

Outcome: *All our cases did challenge us, but we were able to finetune & tailor the treatment.*

Keywords: Diabetes, Pre-Diabetes, Type 5 Diabetes, Geriatric Syndrome, Insulin Resistant, Obesity, Vit D Deficiency, Sleep Deprivation, Early Menarche & T2D Risk, PM 2.5 Pollution, Waist Circumference, Waist to Height Ratio, Liver Health in Glycemic Control

Abbreviations

- **T2D:** Type 2 Diabetes
- **LADA:** Latent Autoimmune Diabetes in Adults

Introduction

Diabetes diagnosis and management in India face challenges of limited access to healthcare, low awareness, financial burdens, and adherence issues which are more pronounced in rural areas & among certain socioeconomic groups, cultural & dietary in-

fluences and physicians' limited time and knowledge also play a role [1].

The global prevalence of diabetes has significantly increased, rising from 200 million in 1990 to 830 million in 2022, with most cases being type 2 diabetes. The rise has been more rapid in low- and middle-income countries. This increase is linked to factors like urbanization, aging populations, and decreased physical activity, along with increased overweight and obesity [2]. The World Health Organization (WHO) alerts that more than half of people living with diabetes are not receiving treatment. Every day, 10,000 people turn 65 globally and the diagnosis & prevalence of diabetes is higher among these aging individuals [2]. In India with an estimated mid-year population of 1464 million in 2025, and 70% of them over 18 years, the rate of diabetics works out to be 526/10000 population. India's population over 60 years old, is around 158.7 million & that keeps increasing. About 30% of the elderly population comprises of diabetics, numbering about 55 million. Add to that another 52 million (over 4 in 10 adults) living with undiagnosed diabetes leading to delayed treatment & complications [1]. Therefore, both primary health care providers and any specialty of medicine practitioner, sees more & more diabetic older adults, impacting how older diabetics cared in India. [5].

Most Indians know that Type 2 diabetes is strongly linked to unhealthy lifestyles, including poor diet, lack of physical activity, and obesity apart from the risk Factors of Ethnicity, age, family history, & genetic factors. People also know that uncontrolled blood sugar levels lead to serious health complications, like heart disease, stroke, kidney disease, nerve damage, and vision loss. But there are some other issues or linkages which influence diabetes diagnosis and management and very few people know and consider in treatment practice. These include i) onset diabetes, ii) Menstruation link to underdiagnosis, iii) linkages between Sleep Deprivation, iv) diabetes in elderly and Aging syndrome, v) Environmental pollution with PM 2.5 Pollution, vi) Vitamin D deficiency, & vii) Age-specific body weight. All these influence prevalence diagnosis & demand changing management practices.

This article tries to review the current understanding of some of these issues and throw light on the update and desired changes in management practices.

Discussions

Pathophysiology

Diabetes is a lifelong condition that causes a person's blood glucose level to hover over normal range of 110-140mg/Dl. Among humans the hormone Insulin produced by the pancreas is responsible for controlling the amount of glucose in the blood round the clock. Diabetes results either due to i) the pancreas doesn't produce any insulin called Type 1 diabetes and ii) where the pancreas doesn't produce enough insulin or the body's cells don't react to insulin- type 2 iii)) Latent Autoimmune Diabetes in Adults (LADA) develops in adulthood and gradually, but it involves an autoimmune process like Type 1 diabetes [2]. All these situations result in glucose staying in the blood & aren't used as fuel for energy. It is often associated with obesity. While more than 50% of India's population is estimated to be below the age of 25 and more than 65% to be below the age of 35.

Linkage with Onset of Diabetes

Type 2 diabetes can develop at any age, including childhood, but it's most diagnosed in middle-aged and older people. The risk of developing type 2 diabetes increases with age, particularly during middle age (45-64), due to a combination of genetic predisposition, lifestyle factors of being overweight, having high blood pressure, and lack of physical activity, and changes in the body's ability to produce and utilize insulin as we age. It's also becoming more common among younger individuals, including children and teens. The average age of individuals developing diabetes in India is typically around 45 to 50 years. Some studies have reported the average age of onset to be as low as 42.96 years, while others indicate it's around 50.9 years. A significant portion (around 46%) of type 2 diabetes patients in India are diagnosed under the age of 40. Late-onset (> 40 years) T2D usually presents with gradual, subtle symptoms like increased thirst, urination, hunger, fatigue, blurry vision, numbness or tingling in hands and feet, slow-healing wounds & unexplained weight loss, making early detection challenging [3,4].

Early & Late Onset of Diabetes Type 2

Type 2 diabetes is generally considered to be early onset if it begins in individuals over 18 years and under 40 years of age and onset beyond 40 years is termed as late onset. Onset before 18 years is known as diabetes in children & adolescents [1]. The prevalence of early-onset type 2 diabetes has been increasing in recent years. Women have also been found to be more susceptible to early-onset Type 2 diabetes. Some research studies use age cutoffs to define "late onset" diabetes, as 60 years and above, to compare and analyze the relationship between age of onset & complications.

T2D & Latent Autoimmune Diabetes in Adults (LADA) are different entities. LADA can develop in adulthood and gradually, but it involves an autoimmune process like Type 1 diabetes [2].

Sex Bases Inequalities

The Link between Menstruation & Type 2 Diabetes

While receiving an accurate and timely diagnosis ensures that women & men initiate the treatment & counselling to manage their type 2 diabetes to avoid long-term complications, like heart disease, where sex-based inequalities in care already contribute to poorer outcomes for women. "Use of HbA1c levels for the diagnosis of type 2 diabetes in women younger than 50 (pre-menopausal) years leads to underdiagnosis, owing to the effects of menstrual blood loss on HbA1c readings, shows the first study of its kind. Nearly additional 17% of undiagnosed women younger than 50 years could be reclassified as having type 2 diabetes. Women under 50 had an A1c markedly lower than that of men under 50, by a mean of 1.6 mmol/mol [2].

A study reported that A1c levels in women under 50 years are consistently lower than those in men, which reach the equivalent of those in men up to 10 years after Menopause. Compared with men, women with type 2 diabetes have poorer glycaemia control; a higher risk for CVD complications; reduced life expectancy, a higher risk factor burden, of obesity & hypertension at diagnosis [2].

Another research published Dec. 5, 2023, in the BMJ Nutrition Prevention & Health, suggests that Menarche at an early age in-

creases the risk of developing type 2 diabetes in later life, and is also associated with an increased risk of experiencing a premature stroke, among women attaining menarche before 10 years of age. Such women had a significant association with stroke among women aged under 65 years with diabetes, even after adjusting for the aforementioned factors with an adjusted odds ratio for stroke of 2.66 [3].

Care of Elderly Diabetics

Every day, globally 10,000 people turn 65 and the diagnosis and prevalence of diabetes is higher in aging individuals. In India we have about in 2025, approximately 11.1% of India's population is projected to be over 60 years old, numbering to around 158.7 million & that keeps increasing. About 30% of this elderly population comprises of diabetics, numbering about 55 million. So, we are seeing a shift and GPs or any specialty of medicine one practices, they are going to see more and more diabetic older adults and impacting how we care about our older diabetics. [5]. As per the results of a large-scale survey conducted across India, over 43% of the respondents who had diabetes in 2021 were above 60 years of age and about 3.3% of respondents in the 20- to 29-year-old age bracket also reported to have diabetes that year [7].

Geriatric Syndrome

Geriatric syndrome is basically a group of conditions like cognitive dysfunction, depression, functional or physical impairment, dependency, chronic pain, incontinence, and polypharmacy, which exhibit with aging & higher diabetes prevalence [7].

It is important to identify these comorbid conditions because, clinicians, intuitively don't think about them as they are not a part of our macrovascular or microvascular complication cohort. These conditions are so subtle that often, patients or their caregivers don't recognize them. But they do impact patients' ability to perform self-care and manage their complex therapy [5]. Comorbidities like cardiovascular conditions or stroke or cancer in geriatrics are competing comorbidities. How important is diabetes management for such patients, considering the impact of these comorbidities on life expectancy and quality of life? Diabetes is a bit different in that the goal for glycemia has upper level and lower level, unlike biomarkers in other chronic conditions. Therefore, the practitioner must think about what the goal should be for any individual, considering the benefits of lowering the high glucose and the risk of going too low. The benefit of lowering high blood glucose is typically avoiding long-term complications vs low glucose, which causes poor outcomes such as falls, fractures, a decline in cognition, or even cardiac events. Among elderly in the 80s and 90s, the risks of having low blood sugar & having a fall and fracture and ending up in a nursing home are much more worrisome than a concern about long-term complications that they may not have time to develop. The other side is of how overtreatment or the complexity of the regimen impacts a patient's quality of life, like stress & the difficulty of following those regimens, which impact their and their caregiver's quality of life. In geriatrics, the risks of keeping HbA1c under 7%, with multiple medications have a high risk for hypoglycemia! Gradually, educating the patients is the logic behind relaxing the goal of keeping their A1c under 7%? And the fact that it is making sure that the benefits of the treatment remain without the risk of the aggressive treatment. Clinicians must explain to them the fact that it takes 20 years for high blood sugar to have a major impact, whereas hypoglycemia can be dangerous today! Recent research confirms that A1c is a poor surrogate for the risk of hypoglycemia. Mean glucose does not show how many times or how long the person spends in low blood sugar. Use of continuous glucose monitoring (CGM) helps monitoring intraday variations. When A1c is measured, we measure the glycation of the red blood cell molecule, presuming that the normal lifespan of RBC is 3 months. If the RBC molecule does not live for 3 months, the value of A1c is not appropriate to reflect the true glycemia. Highly prevalent conditions like anemia, blood loss, and acute infection make HbA1c value unreliable in Indian older populations, making HbA1c in-appropriate for treatment changes. Having a professional CGM, which gives just a 2-week pattern, can show the clinician and the patient how much time they're spending in low glucose. We need to be concerned about the other issue most older adults are really worried of cognitive impairment, as the brain only uses glucose to function to convince them not to go overboard, in controlling Hb1Ac if there is no benefit of doing tight control. With CGM, the worst the patient can do is inappropriate use, and if that happens, one can continue to educate them, instead of taking it away.

An insulin pump or the automated insulin delivery (AID), can cause bigger problems when people start getting multiple hypoglycemic episodes, and the caregivers are stressed about that. Most type 1 diabetes patients like independence from monitoring & multidose insulin, explaining to them why the technology is not only working for them, but it's also hurting them and taking them off the technology would be better option.

PM2.5 Pollution Linked to Type 2 Diabetes Risk

Centre for Chronic Disease Control and AIIMS physicians in Delhi and Chennai, India have discovered a relationship between prolonged exposure to PM2.5, and an increase in T2D. The analysis conducted independently for Delhi and Chennai due to the significant disparities in exposure levels. In Chennai, the average exposure level ranges from 30 to 40 micrograms per cubic meter, while in Delhi, it is more than double that and varies between 82 and 100 micrograms per cubic meter.

Data on 9,000 individuals chosen from the public were gathered beginning in 2010 and 2011, every recruit was approximately 45 years old, and six years later, final evaluation was done. Their eating habits and physical activity were observed. All subjects were exposed to pollution at the same level as the surrounding air.

The findings revealed a heightened risk of diabetes development among individuals with hypertension in Chennai. In Delhi, a higher risk of developing diabetes was observed among the younger population under 50 years of age.

It was hypothesized that diabetes & glucose intolerance are brought on by oxidative damage and increased inflammation brought on by exposure to PM 2.5 pollution. It raises the risk factors for cardiovascular illnesses such as heart failure, atherosclerosis, myocardial infarction, diabetes, hypertension, and other cardiovascular disorders [10].

Sleep Deprivation Ups Type 2 Diabetes Risk

Habitual short sleep duration was associated with an increased risk of developing type 2 diabetes, association persisted even

among participants who maintained a healthy diet reported a recent study. In this study of 247,867 adults in the UK Biobank during May-September 2023, with median a follow-up of 12.5 years and association was studied.

Sleep duration was categorized by hours/day as normal (7-8), mildly short (6), moderately short (5), and extremely short (3-4). Dietary habits were based on the consumption of red and processed meat (less healthy) and fruits, vegetables, and fish (healthier), with scores ranging from 0 (unhealthiest) to 5 (healthiest). The results showed that proportions reporting normal, mildly short, moderately short, and extremely short sleep durations were 75.5%, 19.8%, 3.9%, and 0.8%, respectively. Proportions attaining diet scores of 0, 1, 2, 3, 4, and 5 were 1.5%, 7.4%, 17.6%, 27.5%, 29.0%, and 17.0%, respectively. During follow-up, 3.2% (n = 7905) of participants were diagnosed with T2D.

Compared with those with normal sleep duration, adjusted hazard ratios for developing T2D were 1.16 (P = .003) for 5 hours and 1.41 (P < .001) for 3-4 hours, whereas the difference for 6 hours was not significant. Compared with the least healthy diet score of 0, the risk for T2D was significantly lower for those with score of 4 (adjusted hazard ratio, 0.82; P = .01) or 5 (0.75; P < .001). There were no multiplicative or additive interactions between sleep duration and healthy diet scores. Even among those with healthy diet scores of 4-5, adjusted hazard ratios for T2D were significantly elevated for sleep durations 5 hours (1.17) and 3-4 hours (1.46).

The Researchers concluded that a lack of sleep contributes to the development of T2D through i) impaired cellular insulin sensitivity, ii) a skeletal muscle energy metabolism shifted towards non-glucose oxidation, iii) increased activity of the sympathetic nervous system, and iv) altered gut microbiota composition". They also opined that further research is necessary to explore if any specific dietary patterns, such as time-restricted eating, can counteract or alleviate the adverse metabolic consequences associated with short sleep duration [11]. This study alerts clinicians to explore the adequacy of sleep in their patients and resolve if there is any problem.

Link Between Vitamin D Levels and Diabetic Peripheral Neuropathy

A cross-sectional study carried out by researchers at Beijing Hospital suggests a correlation between vitamin D deficiency and the susceptibility to diabetic peripheral neuropathy (DPN) in older adults diagnosed with T2D. The study involved 230 older patients with T2D for 15 years. 175 of them were diagnosed with DPN of whom 169 patients were found to have vitamin D deficiency, characterized by serum 25-hydroxyvitamin D levels below 20 ng/mL. An analysis of large nerve fiber lesions using electromyography, and small nerve fiber lesions evaluated by measuring skin conductance.

Results indicated a higher prevalence of DPN among patients having vitamin D deficiency compared to those without. Vitamin D deficiency appeared to predominantly impact large fiber lesions, as evidenced by longer median sensory nerve latency, minimum latency of the F-wave, and median nerve motor evoked potential latency in the deficient group compared to the vitamin D-sufficient group. A correlation between vitamin D deficiency and large fiber neuropathy, was also noted with an increased likelihood of motor nerve latency prolongation. However, electrochemical skin conductance, indicative of small nerve fiber damage, showed no significant difference between patients with and without vitamin D deficiency.

Study being a cross-sectional design, it hindered establishing a causal relationship, but Vit D supplementation in diabetic nerve damage may be tried by interested Researchers [12].

Age-Specific Body Weight Ranges of T2D Patients and Cardiovascular Risks

A recent study presented at the European Congress on Obesity (ECO 2024) revealed that the optimal body weight ranges for adults with type 2 diabetes (T2D) to minimize their risk of cardiovascular disease-related mortality. Analyzing data from the UK Biobank, researchers found distinct age-related differences in the association between body mass index (BMI) and cardiovascular death risk among 22,874 participants with T2D.

For individuals aged 65 years or younger, maintaining a BMI within the normal range of 23–25 kg/m² was linked to the lowest risk of cardiovascular mortality. In contrast, those over 65 years old experienced the lowest risk if moderately overweight with a BMI of 26–28 kg/m².

The study revealed a U-shaped relationship between BMI and cardiovascular death risk. It highlighted higher risks for both underweight and obese >27 kg/m² for the elderly. It pointed that the waist circumference and waist-to-height ratio emerged better indicators of cardiovascular risk, with increasing measurements correlating with elevated risks of CVD death across both age groups.

Conquering Prediabetes

Prediabetes is a well-established risk factor for progression to diabetes mellitus and is associated with increased risks of vascular complications.[1] A nationwide study in India (ICMR–INDIAB-17 study), encompassing both urban and rural areas across nearly all states, reported a prediabetes prevalence of 15.3%. T2DM can be effectively prevented through targeted interventions during the prediabetic stage. Advancements in prediabetes therapy in India: Insights from The Association of Physicians of India guideline. The management of prediabetes must be multifaceted, incorporating lifestyle interventions, pharmacotherapy, psychological support, and education programs.

Pharmacological Interventions

The threshold for the action of pharmacological therapy should be determined by i) Severity of hyperglycemia, self-perception of severity, susceptibility to worsening of dysglycaemia, developing diabetes, developing cardiovascular complications, or having a positive family history and economic support.

Metformin helps to reduce the risk of T2DM in patients with impaired glucose tolerance (IGT), after lifestyle intervention fails to reduce body weight and improve glucose tolerance. A dosage of 250–850 mg/day Metformin is recommended for patients who have i) a BMI of >35 kg/m2, ii) are 60 years of age, iii) women with h/o gestational diabetes [13]. Other drugs like

Orlistat, Pioglitazone, Acarbose, Nateglinide, and Liraglutide have also demonstrated benefits in reducing the risk of T2DM.

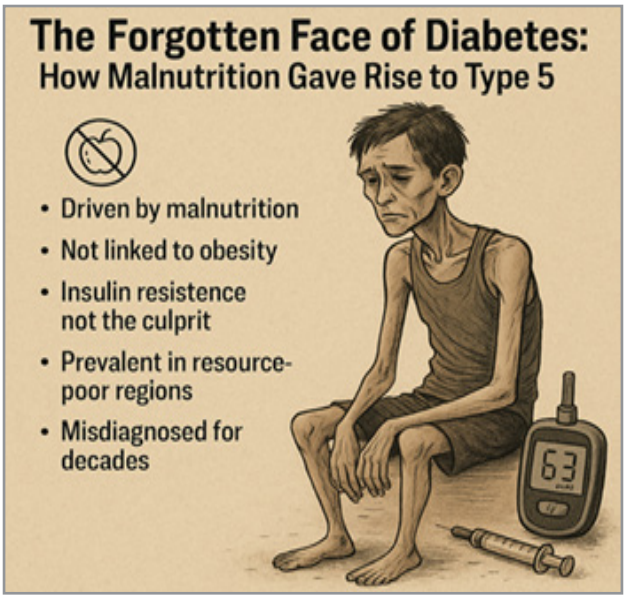
Surgical intervention: Bariatric surgery, another effective method of treating prediabetes, is recommended for individuals who have a BMI of >32.5 kg/m2 with comorbidity or have a BMI of >37.5 kg/m2 without comorbidity, unable to reduce weight even under supervision. Commonly performed procedures include Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, sleeve gastrectomy, and duodenal switch with biliopancreatic diversion [14,15].

Liver Health to Optimize Glycaemic Outcomes in Early Type 2 Diabetes

A study published in the journal Diabetes, Obesity & Metabolism. Reports that liver health plays a significant role in achieving sustained normalization of A1c levels in individuals with early type 2 diabetes. During the maintenance period (from 3 weeks to 2 years), participants achieving sustained A1c normalization had greater reductions in adiposity (BMI: $p = 0.02$; waist circumference: $p = 0.02$), hepatic insulin resistance (HOMA-IR: $p = 0.02$), and ALT levels ($p = 0.005$), suggesting a relative stabilization of beta-cell function and glucose levels. A novel finding was the significant role of reduction in Alanine Aminotransferase (ALT) as an additional determinant, underscoring the liver's critical and independent contribution to sustained glycemic control in persons with early type 2 diabetes, apart from lower baseline A1c and greater reductions in central adiposity for achieving A1c <6.0% at 2 years. This highlights the potential importance of targeting hepatic insulin resistance and liver health in the management of type 2 diabetes. Further research into this association could improve treatment strategies for patients with type 2 diabetes [16].

Forgotten Face Diabetes- Malnutrition and Type 5

Type 5 diabetes has been recently recognized by the International Diabetes Federation (IDF).



It primarily affects lean, undernourished adolescents and young adults in low- and middle-income countries. First identified decades ago but long overlooked, this condition has finally earned its place in global medical classifications giving millions a name, a voice, and a chance. A lifetime of food scarcity starting in the womb leads to irreversible pancreatic damage and inadequate insulin production. These patients are typically underweight, with a BMI below 18.5 kg/m² and little to no body fat. The core issue lies in poor insulin secretion, not resistance, making standard insulin risky. Nutritional rehabilitation, protein-rich diets, and tailored glucose management protocols are key interventions. A global response needed to be seen beyond calories & carbs that addresses the core issue of poverty [17].

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