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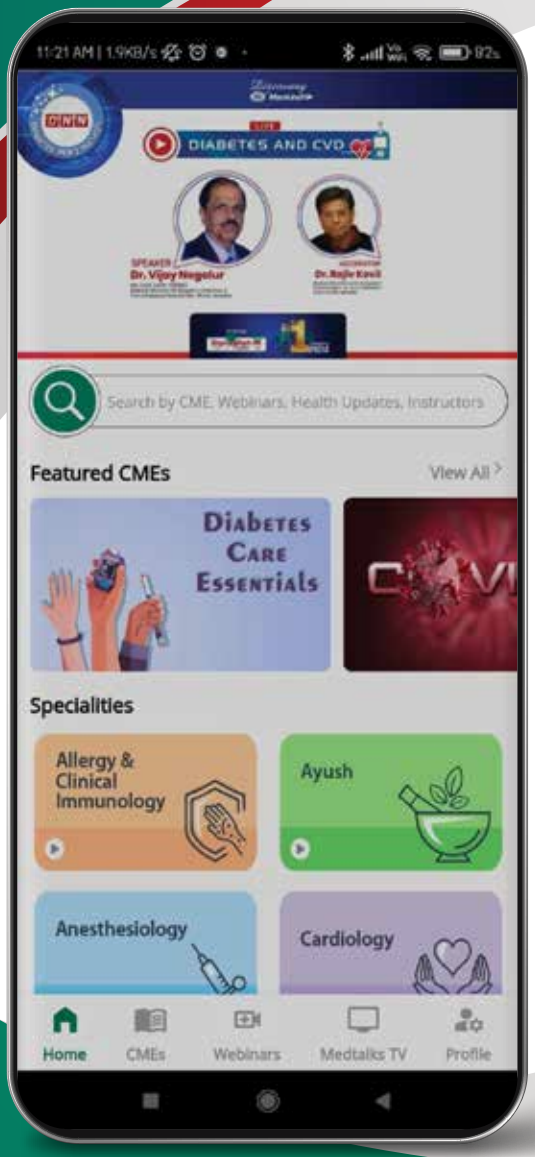

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GUEST EDITORIAL

REVIEW ARTICLE

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The Paradox of Plenty: Caution Against Complacence

A B S T R A C T

Diabetes mellitus is a disease of paradoxes. The focus on diabetes prevention has not halted the increasing incidence of new disease. Newer and better drugs for glucose control and cardiovascular protection have neither improved glucose nor cardiovascular outcomes. This brings in focus the concept of "Quadruple of Atreya" which focuses on an educated cooperative patient in addition to the physician, the drug and the caregiver. Another current paradox is the easy availability of information which includes useful, useless and information intentionally designed to misguide. This year's theme for world diabetes day, "education to protect tomorrow" appreciates this need for patient education today to improve outcomes tomorrow. We are not only urged to educate to improve outcomes but also urged to contest misinformation at its source leading to 'quinary prevention". The harvest of these measures at education and preventing misinformation will lead to better outcome tomorrow analogous to the concept of "metabolic karma" wherein today's actions will have bearing on the future.

Keywords: Quinary prevention of diabetes, World Diabetes Day, diabetes education, metabolic karma, misinformation

Introduction

Diabetes mellitus is a syndrome of paradoxes. While we invest more and more in preventing diabetes, its incidence is increasing.[1] Though we have more and more drugs to manage diabetes, mean glycated hemoglobin (HbA1c) levels remain high. And despite developing multiple cardioprotective drugs, avoidable cardiovascular morbidity and mortality continue to prevail in persons living with diabetes.[2]

This is the paradox of plenty, mere availability of effective diagnostic, monitoring and therapeutic tools does not ensure effective management of diabetes. Just as a vehicle needs a trained qualified and experienced driver, diabetes care requires persons living with diabetes, and their care providers, to be well-versed in their work.

Education is Empowerment

The first step towards this is education. The concept of education has been present in medicine from time immemorial. The Charaka Samhita describes the Quadruple of Atreya, which includes a cooperative patient as one of the four pillars that uphold therapeutic success.[3,4] The other three members of the 'therapeutic quadriga' are the physician, the drug, and the patient's sattendant (caregiver).

Challenges are Plentiful

This, however, is easier said than done. The paradox of plenty comes back to haunt us, yet again. The number of stakeholders in diabetes care is rising, and rightfully so. The complexity of diabetes management has increased and so has the knowledge required to use available medication in a safe and smart manner. Proliferation of social media and other communication channels has increased the spread of information, and misinformation simultaneously.[5]

The Theme

The theme for World Diabetes Day, 2022, acknowledges and appreciates this need for education. "Education to protect tomorrow's"[6] underscores the need for person-centred therapeutic education, the necessity of quinary prevention, and the novelty of metabolic karma.

Person Centred Care

Modern medicine uses the phrases person centred care 'or' patient centred care', along with 'therapeutic patient education', to describe the importance of educating and involving persons living with diabetes regarding their self-care and management.[7,8] Person centred therapeutic education empowers the person living with diabetes to take optimal care of oneself, and protect oneself against avoidable complication.

Metabolic Karma

The phenomenon of glycemic legacy or metabolic memory has been documented in various long-term trials, the most recent being the 44 year long follow-up of the UKPDS (United Kingdom Prevention of Diabetes Study).[9] This finds resonance with Asian philosophy, which describes the occurrence of 'karma' (Sanskrit/Hindi) or 'vipaka' (Sinhala) as past, present and future actions, all of which have a bearing on each other.[10] This is true in diabetes education as well, what one learns today influences one's tomorrow as well, hence, today's education protects tomorrow's health.

Quinary Prevention

The ease of communication that we enjoy, thanks to various social media and e-based messaging, has opened up another paradox of plenty. While the flow of information has certainly eased, so has the spread of misinformation. Fake news appears to fly at the velocity of light.

Inaccurate knowledge can harm health in general, and diabetes care in particular. Quinary prevention, a construct beyond primary secondary tertiary and quaternary levels of prevention, calls for preventing misinformation, and promoting the right education, as a part of health care delivery.[11] There is no room for complacence: we need to keep working to ensure that we protect the today, as well as tomorrow, of our fellow citizens.

Editorial Policy

At the Asian Journal of Diabetology, we endeavor to educate, to empower, to enrich. Through insightful editorials, original research articles, interesting case series/reports, and comprehensive reviews, we share meaningful knowledge about diabetes, so that it can be disseminated to other health care professionals, through them, we hope to reach all persons living with diabetes, and protect them from the complications of diabetes.

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Overweight and Obesity: Opening an Opportunity for Health

A B S T R A C T

Obesity is now recognized as a disease and is often preceded by an overweight status in its natural history of development. Though excess fat is often associated with morbidity, stigma and mortality, this editorial provides a unique perspective of identifying obesity and overweight status as a window of opportunity. The authors reflect how people living with obesity can be identified, motivated and managed, to ensure optimal comprehensive health.

Introduction

Overweight and obesity, two frequently used words, are defined as abnormal or excessive fat accumulation that may impair health.[1] These medical conditions can be easily identified in clinical practice by measuring body mass index (BMI). This is calculated by dividing an individual's weight (kilogram) by the square of his/her height (meters squared).[2] Indian standards define overweight as a BMI ≥23 kg/m^2, and obesity as a BMI ≥25 kg/m^2.

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Outside Asia, however, the thresholds used to define overweight and obesity are 25 and 30 kg/m^2, respectively. In children aged 5 to 19 years, age-specific BMI cut offs are used, while in younger children, weight-for-height ratios are calculated to assess weight health.

The Weight of the Problem

India shoulders a heavy burden of obesity. In a recently published study by Verma et al, based on the National Family Health Survey data, about 30-40% of the Indian adult population was found to be overweight or have obesity.[3] Moreover, a rapid increase in the prevalence was noted across all states of India.

In another recently published study by Sridharan et al, about two-thirds of elderly postmenopausal women from rural south India were found to have obesity.[4] Data have also shown a consistent increase in BMI

Table 1. The Impact of Obesity

Domains	Examples
Metabolic	Diabetes, hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, gallstones, fatty liver
Musculoskeletal	Osteoarthritis, osteoporosis, sarcopenic obesity
Mood	Depression, anxiety, social stigma, eating disorders
Mirror-related (Cosmetic)	Acanthosis nigricans, hyperpigmentation
Malignancy	Endometrial carcinoma, breast cancer
Menstruation/Maternity-related	Polycystic ovary syndrome, infertility
Masculinity-related	Oligospermia, hypogonadism
Monetary	Greater health expenditure
Mortality, premature	Greater risk of death

in children over the past few decades. In a recently published study by Dabas et al from Delhi, the mean BMI in children has increased by 1.2 kg/m^2 over the last decade.[5]

The Impact of Obesity

Obesity has been declared as a disease by the American Medical Association. Overweight and obesity present with multiple complications and comorbid conditions. The impact of obesity can be classified using the 9M mnemonic (Table 1). The cumulative burden of obesity-related complications is mind-boggling. A total of 200 comorbidities have been described in people with obesity. These not only reflect the associated medical problems in people with obesity but also the fact that people living with obesity may approach varied healthcare specialists with obesity-related complications.

Though the metabolic comorbidities of obesity are well recognized, nonmetabolic complications, especially those related to psychosocial outcomes, are often neglected. In a recent study from south India, it was found that 30% of individuals attending a multidisciplinary obesity clinic had an underlying psychological disorder.[6] In addition to the listed comorbidities, today; the management of obesity is focused on the overall well-being of the individual. It is essential to assess the impact of obesity on the health-related quality of life in these individuals. In a recently published study by Ramasamy et al, the majority of the patients attending an obesity clinic were found to have poor quality of life. This was due not only to their medical comorbidities and social stigma, but also because of intrusive therapeutic interventions and strict dietary measures.[7] A person-centered approach to weight management is required, therefore, to offset such distress.[8]

Our Attitude Towards Obesity

Since traditional times, obesity has been viewed as a marker of prosperity and health. While this viewpoint may have had a rational backing during times of famine, it holds no water now. Obesity is clearly linked with excessive biopsychosocial morbidity, healthcare costs and mortality, and needs to be addressed.[9] At the same time, an extreme counter-reaction-obesity stigma, characterized by body shaming and "baro-bullying", seems to be gaining traction.[10]

As a mature society, we need to balance the need for weight control with a respectful approach to individual circumstances and preferences. In this, the lead needs to be taken by physicians, who influence the society's thinking and actions. It is also important to recognize obesity as an opportunity, to screen, identify and manage the associated comorbidities so as to improve the quality of life, prevent further morbidity and mortality.

There are several rights and responsibilities, to be known for a patient with obesity and the treating physician. The key rights for a person with obesity include to be able to acquire sustained and sustainable health, to restore physical and cardiometabolic health and to ensure rescuing psychological well-being. However, at the same time, the patient must also understand that obesity-related comorbidities need time and consistent efforts to resolve and the quick-fix methods do not lead to long-term sustainable outcomes. Persistence and patience are required, both on the patient and the physician's side. Often the first important milestone that is achieved in these patients is halting or cessation of further weight gain.

From the physician's standpoint, the key responsibilities include to be respectful to the patient. Avoid body shaming and understand obesity as a disease state rather than a voluntary choice of the patient. A physician may help to improve this by providing weight friendly infrastructure in the clinic and use a nonstigmatizing language while conversing

Table 2. The AEIOU Hierarchy of Health Literacy and Obesity Care

Accept and acknowledge that obesity is a disease
Explore and evaluate the cause and effect of obesity
Introspect and internalize that action is needed for prevention and care
Open a window of opportunity: Offer options for prevention and management
Understand that obesity care is a lifelong process, in which the entire society must be involved

with patients with obesity. The physician should also take the responsibility of reducing the patient's long-term health-related expenditure and be a role model for others.

One Step at a Time

We must understand that we have a right, and a responsibility, to control our collective weight.

The first step towards this is to accept that obesity is a disease. Once this is done, we must explore and evaluate the reasons for this, in individual patients, and in the society as a whole. Introspection will help internalize the need for action, and allow the healthcare system to offer various options for prevention and management (Table 2).

Nonpharmacological options that are available for obesity management include intensive behavioral therapy, coupled with medical nutrition therapy and structured physical activity.[11] Drugs available in India include orlistat, liraglutide and semaglutide. Liraglutide and semaglutide are glucagon-like peptide-1 receptor agonists (GLP-1RAs) that can be used, in varying doses, for the management of both obesity and diabetes.[12]

An Opportunity for Improvement

These offerings should be viewed as an opportunity to improve current as well as long-term health, and to understand the need for life-long "baro-vigilance". One must also guard against nonvalidated therapies that are not backed by proper clinical trials.

Once our health literacy expands to include the importance of obesity prevention and care, we will be on our way to becoming a healthier nation, to becoming "The Metabolic Care Capital of the World".

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REVIEW ARTICLE

Alcohol Use Disorders and Diabetes Mellitus

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ABSTRACT

Alcohol use disorder is a chronic relapsing brain disorder and is associated with high mortality and morbidity. Chronic alcohol use worsens diabetes and associated diabetes-related complication. Alcohol use, especially over the long-term, can impact the glycemic control in persons with diabetes mellitus. Heavy consumption of alcohol in people with diabetes can lead to worsening of diabetes-related complications like diabetic ketoacidosis, altered lipid metabolism, peripheral neuropathy, sexual dysfunction and cardiovascular disease. This review aims to describe the association between alcohol use and glucose tolerance, effects of alcohol on the pre-existing diabetes; association between alcohol use, diabetes mellitus and diabetes-related complications and interaction of medicines used to treat diabetes with alcohol.

Keywords: Alcohol, alcohol use disorders, diabetes mellitus, insulin, glycemic control

Introduction

Diabetes mellitus affects 537 million adults globally and a substantial proportion of them are from low- and middle-income countries. In 2021, diabetes accounted for 6.7 million deaths worldwide.[1] Alcohol is responsible for around 5% of the global burden of disease. Alcohol contributes a substantial burden socioeconomically as well as for the alcohol-attributable diseases. When it comes to middle- and lower-income countries, the mortality and morbidity risks due to alcohol are more in comparison to high-income countries.

Alcohol consumption has been implicated as an independent and modifiable risk factor for the development of diabetes mellitus.[2] Several cohort studies have examined the association between alcohol and risk of developing type 2 diabetes mellitus (T2DM). It has been proposed that there is a U-shaped relationship between alcohol consumption and risk of developing diabetes. While moderate alcohol use may reduce the risk of T2DM,[3] heavy alcohol use increases the risk.[4] In addition, alcohol can have an immediate deleterious effect on diabetes control by worsening hypoglycemia, particularly in individuals using insulin or insulin secretagogues and can also contribute to weight gain.

The current article discusses the association of alcohol intake and glucose tolerance, and the effect of alcohol on blood glucose levels. Furthermore, this article also explores the existing literature on association between alcohol and diabetes mellitus and the pharmacological interventions for alcohol use disorder.

Association Between Alcohol Intake and Glucose Tolerance

Following alcohol consumption in individuals with or without diabetes, the glucose disposal rate as well as insulin secretion are increased. Heavy alcohol use leads to beta-cell dysfunction, which predisposes an

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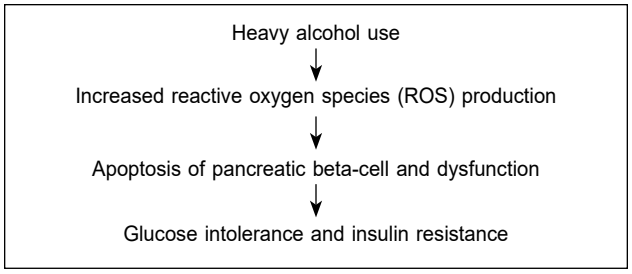

individual to diabetes mellitus. In individuals with alcohol dependence, appetite regulating peptides like ghrelin and leptin are altered leading to insulin resistance further contributing to the development of diabetes mellitus.[5] Common genetic variants have been shown to interact with diabetes and heavy alcohol use.[6]

There are also conflicting results, where some studies state reduced risk of diabetes with moderate alcohol use, some reported nil and some showed positive association.

One of the earliest occurrences in glucose intolerance is the production of ROS.[5] Animal models have also shown a reduction in glutathione following alcohol administration. Glutathione is an antioxidant and helps in fighting free radical production.[7]

In a well-fed state, there is a surge in blood glucose level after food intake. In normal individuals, in the absence of diabetes, there is uptake of glucose in the muscle and fat tissues. The existing glucose is converted into glycogen, which acts as a reserve when there is fall in blood glucose level. In type 1 diabetes mellitus (T1DM), since there is no insulin or minimal insulin production, blood glucose level tends to remain high with gradual impairment in both protein and fat metabolism giving rise to serious complications. In T2DM, on the other hand, there is normal to high insulin production and the body initially tries to resist the effect of insulin. In due course, the body cannot produce enough insulin further giving rise

Table 1. Effects of Alcohol on Blood Glucose Level in Pre-existing Diabetes

Author (Year)	Type of study	Sample size	Mean alcohol use	Times of glucose measurement	Insulin use	Result
Gepner et al (2015)[9]	RCT	68	16 g of white wine	104 weeks	11%	White wine decreased fasting glucose by 1 mmol/L. Improvement in glycemic control was observed.
Gepner et al (2015)[9]	RCT	73	17 g of red wine	104 weeks	13%	No significant decrease in blood glucose level.
Nakamura et al (2009)[10]	RCT	12	12 g of white wine	26 weeks	36%	No significant change in blood glucose level.
Nakamura et al (2009)[10]	RCT	12	12 g of red wine	26 weeks	36%	No significant change in blood glucose level.
Kerr et al (2009)[11]	RCT	10	48-80 g of white wine	2 and 4 hours	Yes	Significant change in blood glucose level after 4 hours.
Bantle et al (2008)[12]	RCT	18	24 g of wine	2, 4 and 24 hours	No	No effect on plasma glucose or insulin level.
Bantle et al (2008)[12]	RCT	17	18 g of wine	4 weeks	No	No effect on plasma glucose or insulin level.
Dalgaard et al (2004)[13]	RCT	11	40 g of ethanol with food	0.5, 2, 4 and 24 hours	No	Alcohol subdues incretin responses in postprandial phase. No significant difference in blood glucose level.
Koivisto et al (1993)[14]	RCT	10	61 g (vodka, red wine and cognac)	0.5 hours	Yes	No significant increase in blood glucose level.
Koivisto et al (1993)[14]	RCT	16	61 g (vodka, red wine and cognac)	0.5, 2, 4 and 24 hours	No	No effect on postprandial blood glucose level. Serum insulin was higher after 3 hours of food and alcohol intake.

to complications.[8] Chronic heavy alcohol use leads to decreased insulin secretion and sensitivity. In an individual with pre-existing diabetes, alcohol can worsen fasting as well as postprandial glucose level. Several randomized control trials have looked into the short-term and medium-terms effects of alcohol on blood glucose level in individuals with diabetes.

In the studies (Table 1), which have examined the effect of alcohol use on blood glucose levels, the dose of alcohol has ranged from 12 to 80 g. Majority of the studies had nonsignificant change in the blood glucose level after alcohol consumption. No adverse events of hypoglycemia and withdrawal were reported in any of the studies.

Light-to-moderate alcohol consumption has no effect on blood glucose level. Another important factor to note is that the average alcohol intake over a short period of time might not capture the changes in blood glucose level. The pattern of alcohol consumption varies and measurement at a single time frame can give confounding results. Also the effect of heavy alcohol use in glucose level in patients with pre-existing diabetes requires research.

Future prospective studies are required to look into the long-term changes associated with alcohol use in pre-existing diabetes.

Association Between Alcohol and Diabetes Mellitus

Many studies have explored the role of alcohol as an independent risk factor for diabetes mellitus. As early as 1971, Phillips et al[15] stated that a mean alcohol dose of 233-516 mg/dL causes insulin resistance and glucose tolerance. Taking this into account further cross-sectional studies also had similar findings. A meta-analysis by Baliunas et al in 2009[16] explored the association of alcohol use and diabetes mellitus, where findings of heavy drinkers (>50 g of alcohol/day in women and >60 g of alcohol/day in men) and nondrinkers were similar. No clear conclusion could be figured from the study.

Leggio et al in 2009 looked into the results from the multisite COMBINE study and evaluated the association between blood glucose level, heavy alcohol consumption and craving for alcohol during the treatment process in a sample of 1,324 patients. Baseline blood glucose level was found to have a positive association with percentage of heavy drinking days during treatment suggesting a role of blood glucose in heavy alcohol use.[17]

A 12-year follow-up study conducted by Lee et al in 2017, which investigated the association of pattern of alcohol consumption and risk of T2DM reported that heavy drinking pattern (>30 g/day) increased the risk of incident diabetes, whereas with light or moderate drinking, the risk was reduced.[18]

A 12-year follow-up study by Jang et al in 2019, which aimed to determine whether longitudinal association between genetic variants of *GCK* (glucokinase) or *INSR* (insulin receptor) in heavy alcohol users was associated with the risk of developing diabetes concluded that the risk of diabetes was increased in chronic heavy alcohol users who had the C allele of *GCK*. Chronic heavy alcohol consumers who had *INSR* haplotype negative also were at a higher risk of developing diabetes mellitus.[6]

Role of Alcohol in Diabetes-related Complications

A systematic review was conducted in 2004 which aimed to look into the effect of alcohol use in incidence, management and complications of diabetes mellitus. Thirty-two studies met the inclusion criteria and affirmed that compared to moderate alcohol use, heavy alcohol consumption was associated with 43% increased risk of developing diabetes mellitus. Two experimental studies looked into the effect of alcohol into diabetic medication-related compilations and found that chlorpropamide (sulfonylurea) was associated with reduced ethanol elimination.[19]

Alcohol can worsen the complications associated with diabetes mellitus and the mechanisms by which it does so areas described below:

- **Diabetic ketoacidosis:** Although ketoacidosis is more common in people with T1DM as they completely lack insulin, nevertheless heavy alcohol use can cause ketoacidosis in a person who is not a known diabetic as well. On prolonged heavy alcohol consumption, an individual usually does not consume food and develops low blood glucose levels and can also reduce gluconeogenesis. However, some may have increased levels as in absence of insulin there is less glucose uptake in the tissues. Two important factors resulting in ketoacidosis are lack of insulin and increased glucagon levels.[8]
- **Altered lipid metabolism:** Individuals with diabetes are prone to develop dyslipidemia. Initial change in liver pathology following daily alcohol use is fatty liver and heavy alcohol use further leads to steatosis, which sensitizes the

liver for further injury.[20] Some of the alterations in lipid metabolism seen with alcohol use are increased triglyceride (TG) level, decreased low-density lipoprotein (LDL) and elevated high-density lipoprotein (HDL). A study by Shimomura et al in 2013 investigated the role of alcohol and lipid parameters in 1,477 diabetic individuals and classified their alcohol use into light, moderate and heavy drinkers. Results showed alcohol intake had an inverse relation with high TG/HDL cholesterol ratio in individuals with light and moderate alcohol use, whereas in heavy drinkers the ratio was higher.[21] Polymorphism of alcohol dehydrogenase, aldehyde dehydrogenase, genes related to lipid metabolism and apolipoprotein E can lead to altered lipid metabolism in individual with diabetes mellitus and alcohol use.[22,23]

- **Peripheral neuropathy:** Clinical presentation of peripheral neuropathy can range from asymptomatic to symptoms such as tingling and numbness, burning sensation and pain, which can be debilitating and is common amongst individuals with diabetes and alcohol use. Diabetic peripheral neuropathy affects small C fibers and to some extent A_{delta} fibers, whereas in alcoholic neuropathy large fibers are involved, which result from thiamine deficiency.[24] Alcohol and diabetes can amplify each other's effect in causing peripheral neuropathy. A study conducted in 1980 looked into the effect of alcohol intake in 541 individuals with diabetes experiencing symptomatic peripheral neuropathy. In this sample, 15% were heavy drinkers and 7% had frank alcohol use disorder and it was found that symptomatic peripheral neuropathy was much higher among the heavy drinkers.[25]
- **Cardiovascular disease:** Chronic heavy alcohol use is associated with hypertension, increased risk of hemorrhagic strokes, cardiomyopathy, heart failure and arrhythmia.[26] The relationship between alcohol in individuals with diabetes and acute coronary syndrome has been described as a J-shaped curve where the risk is lowest among light drinkers (<12 g/day) and highest amongst moderate to heavy drinkers (12-24 g and >24 g/day).[27] The probable mechanisms proposed were increased TG level and decrease in HDL leading to cardiovascular problems.
- **Sexual dysfunction:** Mechanisms underlying erectile dysfunction in diabetes mellitus and alcohol are multifactorial and can be vascular, neurogenic and hormonal. Diabetic neuropathy *per se* worsens the autonomic and somatic nerve processes, which play a role in erection. Low testosterone level has been associated with diabetes mellitus and chronic alcohol use. A study in Japan investigating the pattern of alcohol use causing

Table 2. Medications for Alcohol Use Disorder

Medicines	Dosage	Adverse effects
Naltrexone	50 mg/day	Nausea, vomiting, decreased appetite, abdominal pain (unsafe in patients with liver disease)
Injectable naltrexone	FDA approved injectable naltrexone 380 mg/month intramuscularly	
Acamprosate	1998 mg/day orally in 3 divided doses	GI upset, diarrhea (safe in patients with liver disease)
Disulfiram	250-500 mg/day	Drowsiness, metallic taste, peripheral neuropathy, hepatitis, psychosis, optic neuritis, confusional state
Baclofen	30-80 mg in 3 divided doses Starting from 5 mg 3 times a day and then 10 mg 3 times a day followed by 20 mg 3 to 4 times a day. Titration of dose to be done in 3 to 7 days till treatment goal is achieved. Can be increased up to 180 mg.	Drowsiness, headache, confusion
Topiramate	75-300 mg/day in 2 divided doses	Paresthesia, difficulty in attention and concentration, pruritus, anorexia
Gabapentin	600-1800 mg/day in 3 divided doses	Dizziness, peripheral edema, gait disorder
Nalmefene	5-80 mg/day in once daily or twice daily dosing	Nausea, vomiting, headache

Table 3. Interaction of Medicines Used to Treat Diabetes with Alcohol

Medicine	Mechanism	Studies
Chlorpropamide (sulfonylurea)	Inhibits aldehyde dehydrogenase in the brain and liver. Can cause disulfiram-like reaction (flushing, nausea, vomiting, sweating) if taken along with alcohol.	Ohlin et al (1982)[30]
Glyburide	Can cause disulfiram-like reaction if taken along with alcohol.	Johnson & Seneviratne (2014)[31]
Tolbutamide	Increased metabolism of tolbutamide. Can cause disulfiram-like reaction if taken along with alcohol.	Carulli et al (1971)[32]; Kater et al (1969)[33]
Tolazamide	Can cause disulfiram-like reaction if taken along with alcohol.	Jones (2004)[34]
Glipizide	Alcohol delays the absorption and elimination of gliclazide.	Johnson & Seneviratne (2014)[31]
Metformin	Alcohol increases effect of metformin on lactate metabolism.	Schaffalitzky de Muckadell et al (1979)[35]; Dubas & Johnson (1981)[36]
Troglitazone	Worsening of liver function when simultaneously taken.	Johnson & Seneviratne (2014)[31]
Insulin	Alcohol potentiates the action of insulin by lowering the glucose level.	Johnson & Seneviratne (2014)[31]

erectile dysfunction in individuals with T2DM reported a 43% prevalence of erectile dysfunction. Weekly consumption of alcohol <60 g in patients with T2DM was associated with lower erectile dysfunction suggesting an inverse relationship with frequency of alcohol consumption and erectile dysfunction.[28]

Drug Interactions – Alcohol Use Disorder and Diabetes Mellitus

The US Food and Drug Administration (FDA) has approved naltrexone, acamprosate and disulfiram for the treatment of alcohol use disorder.[29] Other non-FDA approved medications like baclofen, topiramate, gabapentin and nalmefene have also been used to treat alcohol use disorder (Table 2).

There can be both pharmacodynamic as well as pharmacokinetic drug interactions of antidiabetic medications with alcohol. Where kinetic interactions occur at the level of metabolism or absorption of the drug, pharmacodynamic interactions primarily occur at the receptor or tissue level. Table 3 describes the interactions of medications used for treatment of diabetes with alcohol.

Future Considerations

Co-occurrence of alcohol use (including alcohol use disorders) and diabetes is a significant clinical and public health issue. The effect of heavy alcohol use in glucose level in patients with pre-existing diabetes needs more research. There are gaps in literature about anticraving agents for alcohol use disorder and medications used for diabetes mellitus. More studies are required to know about the course and outcome, profile of patients and quality of life in patients with diabetes and alcohol use disorder to have a better understanding. Indian studies about this are minimal and need further attention.

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REVIEW ARTICLE

Transition Care in Type 1 Diabetes. Five Questions and Five Principles.

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ABSTRACT

Management of type 1 diabetes mellitus during the period of adolescence to young adulthood is among the most challenging in the field of diabetes care. At around the age of 18 there is a physical transfer of care from pediatric physicians to adult physicians. Alongside there is transfer of responsibility of self-care from parents to the patient over a period of time. Unique medical problems encountered in this age group include puberty induced increase in insulin requirements, an increase in psychiatric comorbidities including substance use and abuse, disconnect with health care teams, and problems related to reproductive care and contraception. This is reflected in the poorer outcomes seen in this age group including an increase in acute complications, increase in hospitalizations with diabetic emergencies, poor glucose control and an increase in loss to follow. The poor metabolic control during this period leads to establishment of early chronic macro and microvascular complications. A structured transition care is a planned purposeful process that address these unique medical, psychological, and vocational needs among these patients that smoothens out the process of transfer to adult care teams. The models that have been proven to be useful in improving outcomes include the use of separate transition clinics, use of transition coordinators and enrollment into young patients support groups. Regardless of the model used there are five overarching principles that define this process of transition care. They can be summarized in five Cs which include: appropriate communication, assessment of self-care needs, building competence, using collaborative teams, and finally providing care and counseling for psychological issues.

Keywords: Transition care, type 1 diabetes mellitus, adolescence, young adults, transfer of cares

Introduction

Diabetes management in our country is a challenging task regardless of the type of diabetes mellitus or associated comorbidities and complications. Among the many complicated patients that are encountered in a diabetic clinic the most challenging in our opinion is the management of type 1 diabetes mellitus (T1DM) during adolescence and early young adult- hood. During this period young patients may encounter a transfer of care from a pediatric endocrinologist to an adult endocrinologist and a transfer of responsibility of day-to-day diabetes care from parents to self (Fig. 1). Additionally, some children may also encounter the need to adjust to a new living situation away from the support of family and friends in a new city as they leave for college, further training, employment, or marriage. Transition of care is distinct from transfer of care among adolescents with T1DM in that it is defined as "a planned purposeful process that specifically addresses the unique medical, psychological, social, vocational and educational needs of these children as they move from pediatric to adult care for chronic lifelong diseases like T1DM" (Fig. 2).[1]

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Q1. Why is Transition Care Needed?

A child or an adolescent diagnosed with a chronic disorder like T1DM must carry the disease into his/her

adulthood and beyond. The primary goal of transition care is to help the child with T1DM to seamlessly shift from a pediatric family centred diabetes care environment to an independent adulthood (Fig. 3). There are several reasons why transition care is essential. These include:

- **Underdeveloped prefrontal cortex in young adults.** Though crossing the age of 18 is considered the threshold of adulthood in most countries it is slowly being realized that complete maturity of the prefrontal cortex only happens in the early twenties.[2] The prefrontal cortex is an area responsible for many of the important cognitive behaviors that are associated with adulthood (Fig. 4).
- **Insulin resistance related to pubertal hormone changes.** Puberty induces a combination of hormonal changes involving the gonadal and growth axis that leads to an increase in insulin resistance. Normal children in late puberty secrete almost double the amount of insulin compared to children in early puberty. In adolescents with T1DM this corresponds to an increased requirement of exogenous insulin and difficulty in achieving glucose targets. Additionally, puberty may unmask dawn phenomenon in many adolescents and girls may note an increase in insulin requirements in the premenstrual period.[3,4.]
- **An increase in psychological issues during this period.** Almost all adolescents struggle during this period where they are developing their identity and autonomy independent of the family. Adolescents with T1DM have to face additional challenges including adhering to insulin and self-monitoring regimes, uncomfortable interactions with peers, classmates and colleagues at work, disagreements with family regarding diabetes self-care, fear of short-term complications like hypoglycemia and hospitalizations and fear of long-term complications and feelings of guilt when glucose control is suboptimal.[5] All these lead to an increase in the prevalence of anxiety disorders, panic attacks and psychological distress.[6] Depression and depressive symptoms are common among T1DM in this age group. In the SEARCH study girls with T1DM had a 10.9% prevalence of moderate to severe depressive symptoms.[7] Eating disorders are 2.4-fold more common among girls with T1DM compared to girls without diabetes of similar age.[8]
- **Sexual and reproductive health issues.** There is no reason for adolescents and young adults with T1DM to behave any differently from their peers without diabetes. All young patients should receive preconceptional counseling and be given appropriate contraception advice.

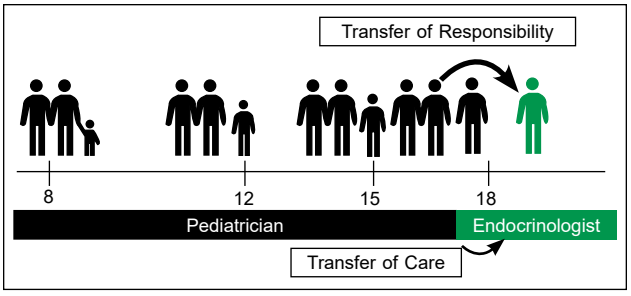

Figure 1. The concept of transfer of care at attaining adulthood among children with lifelong chronic diseases like type 1 diabetes mellitus who need long-term medical supervision and contact. There is also a gradual transfer of responsibility in the day-to-day management of the disease from the parent to the patient at some point during these years.

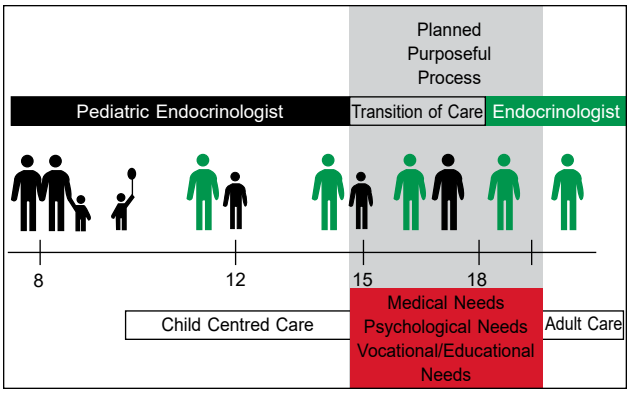

Figure 2. The concept of transition of care is explained as a planned, purposeful process that addresses the specific needs of the patient during this process of transfer of medical care and responsibilities at the attainment of adulthood. The process however starts much before the age of 18 and can continue for as long as it is required.

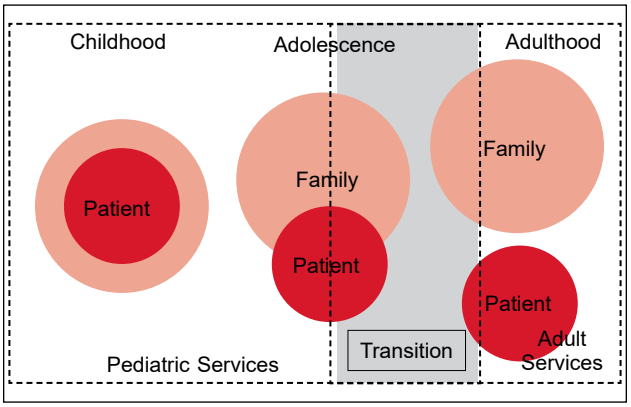

Figure 3. The differences between family and patient dynamics in childhood, adolescence, and adulthood and the placement of transition services.

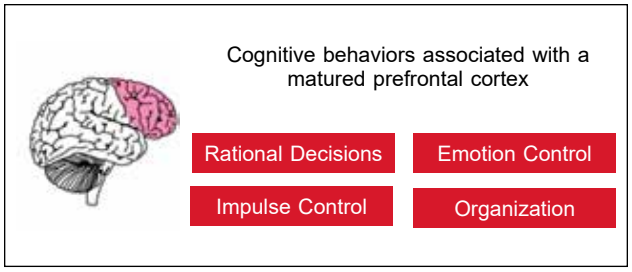

Figure 4. Important cognitive functions and behaviors associated with the prefrontal cortex that take longer than 18 years to attain full maturity.

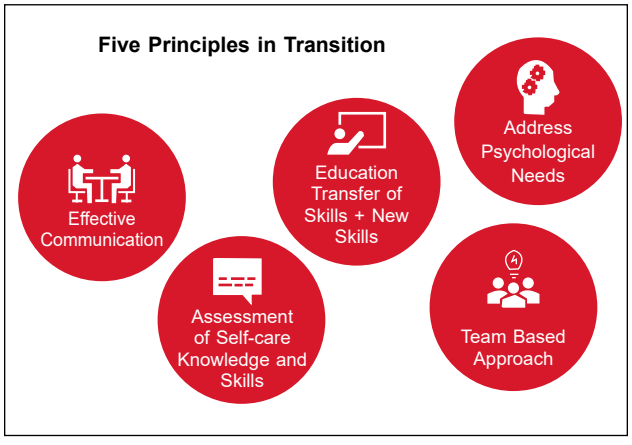

Figure 5. The five primary principles of transition care are summarized in the figure. They can be visualized as the five "Cs" for easy recall. This includes communication, care assessment, competence building, collaboration, and counseling/care for psychological issues.

- **Alcohol, smoking and drug use.** Again, there is no evidence that alcohol, tobacco, and drug use rates are any different among adolescents with T1DM compared to peers who do not have diabetes. Alcohol worsens hyperglycemia immediately and increases the risk for delayed hypoglycemia. All though abstaining from alcohol is the safest response, in practical terms, young people with T1DM need to be educated about safe drinking and decreasing any risks by maintaining hydration, eating adequate carbohydrates, reducing insulin doses if required, and monitoring blood glucose levels.
- **Social, educational, and vocational changes.** Adolescents during the transition period have major changes in their life that includes going for undergraduate or postgraduate studies on occasions to cities far from where they have been brought up in, independent living in hostels and other student accommodations with difficult access to appropriate diets and meals, earning for their livelihood, training and internship which may include shift and night duties and in a small number of cases getting married and starting a family of their own.

Q2. Are Bad Outcomes Noted in the Transition Period?

As noted above, the period of transition is potentially associated with the interruption of a long-term "comfortable" relationship with health care providers especially at a time when the adolescent is confronting multiple issues related to changing metabolism and the development of identity and autonomy. Poor health choices with smoking, alcohol use especially binge drinking, and loss of parental supervision of diet and insulin administration may complicate matters further. The poor outcomes noted during this period include:

- **Poor metabolic control.** Current hemoglobin A1c (HbA1c) targets from the American Diabetes Association (ADA) for children between the ages of 13 years and 18 years is <7.5% (58.5 mmol/moL) and after the age of 19 years is <7% (53 mmol/moL).[9] Most teenagers and young adults struggle to meet these targets. Data from the SEARCH Study in youth with T1DM suggests that only 32% of teenagers (13 to 18 years) and 18% of the young adults (19 onwards) achieved these targets.[10] This stands in contrast with 56% of adults achieving HbA1c targets of <7% (53 mmol/moL).[11]
- **Loss to follow-up.** Transitioning older teenagers and young women are at particularly high-risk of disengagement from health care providers because of the competing distractions. Though there is limited published information about the frequency of contact between young people and health care professionals. Clinic attendance was significantly lower (8.5 ± 2.3/years vs. 6.7 ± 3.2/years) over 3 years when teenagers were transitioned from pediatric to adult services in Germany when compared to previous attendance at pediatric clinics.[12]
- **Risk of acute complications.** A large cohort of 1,243 children (aged from infancy to 19 years) was followed up for 3,994 person-years in Denver. The primary outcome in the study was the rate of acute presentation to emergency department with ketoacidosis and severe hypoglycemia. The overall incidence of diabetic ketoacidosis was 8 episodes/100 person-years in the cohort. The highest incidence of diabetic ketoacidosis was seen among adolescent between the ages of 13 years and 19 years with rates over 12 episodes/100 person-

years.[13] Another study from Ontario looked at 1,507 patients with type 1 diabetes followed for 4 years after transition to adult clinic. The hospitalization rates increased from 7.6 episodes/100 patient-years prior to transition to 9.5 admissions/100 patient-years after transition (p = 0.03).[14]

- **Emergence of chronic complications of diabetes.** Chronic complications related to diabetes are extremely rare among preadolescents. Even among adolescents, clinically apparent diabetes related complications are very rare. Although preclinical evidence of diabetes related microvascular complications maybe present in adolescents. Evidence of early atherosclerotic processes including fatty streaks and intimal lesions are seen in autopsy studies conducted on adolescents and young adults.[15]
- **Premature mortality during transition.** Mortality rates are increased in patients with diabetes compared to the general population at all ages. Within this cohort of patients with diabetes mellitus, men have an increased risk of death compared to women at all age groups except between the ages of 5 years and 15 years. However, the relative risk (RR) of death is much higher in women at all ages. The RR of death (standardized mortality ratio [SMR]) is 4 for women and 2.7 for men. The peak SMR in women was between the ages of 20 years and 29 years at which point it was as high as 5.7. Most of this information has come from a very large cohort of patient with insulin treated diabetes from the United Kingdom.[16]

Q3. What Are the Current Transition Models That Have Been Shown to Work?

Currently, there are no randomized controlled trials examining the overall efficacy of a structured transition program among adolescents and young adults. However, structured transitional care has been demonstrated in cohort studies to have better outcomes in terms of less loss to follow-up, better HbA1c levels, fewer admissions with diabetic ketoacidosis, and fewer long-term complications at the end of the transition.[17,18] There are three basic models which can be followed which have been found to improve outcomes.

- **Dedicated transition or young adult clinics.** The earliest and simplest model appears to be a dedicated transition clinic staffed by both pediatric and adult diabetes teams which handle children in transition for a given period prior to complete transfer of care to the adult diabetes services. Logan et al. from the United Kingdom reported data from a structured intervention that consisted of a year-long transition clinic which comprised of both pediatric and adult physicians and nurses. Patients were seen three times a year and on two out of the three occasions, the patient could choose the provider they wished to see (doctor, nurse, dietician, or clinical psychologist). Over a period of 3 year, patients had an 84% attendance rate, a drop of HbA1c from 9.7% to 9.0% (first to last visit), and a significant increase in percentage of patients with HbA1c less than 7.5%.[19]
- **Transition coordinators.** A second more economical approach rather than having a full-fledged transition clinic is to have a separate transition coordinator. The first use of transitional care coordinators was documented from Australia. The coordinators helped to maintain attendance at the dedicated young adult clinic.[20] A similar Maestro project in Canada used a systems navigator or "maestro" to help access adult medical care as stand-alone in routine pediatric to adult transition patients. Additionally, the intervention consisted of a website, a regular newsletter, group meetings, and access to especially devised young adult educational events. The program was successful in reducing loss to follow-up and helping older transition patients reconnect with medical care.[21]
- **Young adult support group.** Everyone needs a friend in their life, and it is more convenient to communicate with the one who is passing through the same condition as you are. So, forming a young adult group where all these young adults can discuss their issues or even come up with new solutions is yet another way to ease out the transition period. A recent publication has highlighted the utility of support groups for young adults with type 1 diabetes during the transition period. In this study, the participants attended monthly support groups sessions for 5 months. Eighty percent of the participants attended at least three sessions and two-thirds of patients had significant improvements in HbA1c at the end of the program.[22]

Q4. What is the Ludhiana Model of Transition Care?

At Christian Medical College and Hospital, Ludhiana we use a model that utilizes both a transitional care coordinator and a young adult support group. Children are encouraged to enroll into transition between the ages of 15-16 years and continue to be in the transition

group till they are comfortable with our checklist of care/education goals. The transitional coordinator volunteers her time in addition to her primary job as a research associate and helps keep the costs of the care model low. The support group primarily communicates with each other on a WhatsApp group which is moderated by the transitional coordinator. Enrollment into the group is after an informed consent. All transitioning adolescents and young adults have access to a psychologist, but payments must be made if her services are utilized.

Q5. What Are the Primary Principles of Transition?

Regardless of which model is chosen for transition there are some overarching principles that need to be considered when planning out a transition care model. The five principles are summarized in Figure 5. The five Cs of transition are mentioned below:

- **Communication.** You need to communicate with the child. To be a favorable communicator you need to adapt the model of active listening where you understand and respond without invalidating the child's point of view. Ask them about their thoughts on the disease and make them realize the importance of managing it.
- **Care (self-knowledge) assessment.** This includes a thorough assessment of the child's knowledge about diabetes and skills required to manage diabetes on a day-to-day basis. It is usually that the family is accountable for the child's health care prior to adolescence. You can assess their skills through tools like questionnaires in which you can ask about their knowledge about insulin, insulin self-administration, insulin dose adjustments, insulin storage and disposal of sharps. Additionally, skills at self-monitoring, diabetes management if they get sick etc. should be assessed and skills that very likely are available in the family need to be now transferred to the child.
- **Competence building.** Once self-care knowledge is assessed a plan should be made to transfer this knowledge and skills from the family/health care provider to the child. This may include skills like insulin administration, self-monitoring of glucose and dose adjustments to more complicated skills like making doctor's appointments, getting medications in time, and having emergency contacts. New skills that need to be provided during transition include safe driving with diabetes, handling stress at work/schools/examinations, handling peer pressure, safe drinking, and contraceptive advice.
- **Cooperation and collaboration.** The fourth most important principle of transition is realizing that successful transition needs teamwork of health care professionals, family members and friends. Health care teams could include physicians, diabetes specialist nurses, dieticians, psychologists, podiatrists, and transition coordinators.
- **Counseling and caring for psychological issues.** As previously mentioned the period of transition is associated with a variety of psychological issues. Many of these require specialized care and appropriate therapy. Transition teams should be able to make this available to children who require this.

Transition period is a vulnerable time for emerging young adults with chronic medical conditions. As adolescents start moving to a different place to gear up for their independent earning, they lose contact with their health care providers which leads to gaps in medical care. There is a large overlap of psychosocial issues so a team-based approach of primary care and psychology would be beneficial. Transition checklists in the clinics can help to address the problems young adults are facing and can ease up the transition process. Awareness and early initiation with a well-structured process for transition is essential.

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REVIEW ARTICLE

Role of Glimepiride in the Evolving Landscape of Type 2 Diabetes Management

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ABSTRACT

Background and aims: The management of type 2 diabetes (T2D) is complex metabolic syndrome owing to the complex etiological factors linked with the disease. The complex etiological factors affect the disease progression, patient's response to the oral hypoglycemic agents, and the development of micro- and macrovascular complications. Glimepiride is a modern sulfonylurea which has demonstrated high efficacy, cost and practicability of use and is therefore placed among one of the most widely prescribed drugs across the world. In this article, the place of glimepiride in the ever evolving management of T2D is evaluated. **Methods:** Authors conducted a review of published literature to evaluate the role of glimepiride in the management landscape of T2DM. Two recent articles were identified, and backward chronological search was conducted to identify all other important articles. **Results and conclusions:** Based on the selection criteria, 46 articles were selected for the review. The themes that emerged after a thorough assessment of the selected articles comprised of the place of glimepiride in T2D management, its glycemic potency, efficacy, durability, cardiovascular (CV) safety concerns, cost-effectiveness and compliance. It has been established that the use of glimepiride as a second-line agent helps in rapid glycemic optimization and prevention and reduction of diabetes-related complications. Authors have concluded that glimepiride is considered to be a good alternative for T2D management because of its high efficacy, relative CV safety and low-cost.

Keywords: Glimepiride, modern sulfonylureas, cardiovascular outcome, T2DM, CAROLINA trial

Introduction

Diabetes is usually diagnosed based on hyperglycemia; however, several complex etiological factors are at work, which may lead to hyperglycemia. These complex etiological processes not only affect the phenotype of the disease, but also have a considerable impact on the disease progression, response to drugs and associated micro- and macrovascular complications. Type 2 diabetes (T2D), thus, is driven by several pathophysiological processes leading to a spread of clinical characteristics which have a profound effect on how the affected individuals are managed.[1] In the management of T2D, an optimal glycemic control, avoiding acute hyperglycemia, hypoglycemia and glycemic variability may considerably improve the outcome.[2]

Numerous oral antidiabetic agents are in use as monotherapy or in combination therapy for the treatment of type 2 diabetes mellitus (T2DM). Currently, oral antidiabetic drugs (OADs) dominate

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the prescribing pattern, of which metformin alone or in combination with sulfonylureas (SUs) are the most frequently prescribed OADs in many countries. Modern SUs like glimepiride is widely used as second-line agent in the management of T2DM. The use of glimepiride as second-line agent helps in quickly achieving the target glycemic level and reduction of diabetes-related complications. Glimepiride is considered to be a good option in T2D management due to their high efficacy, relative cardiovascular (CV) safety and low-cost. It is also associated with fewer side effects and better efficacy.[3]

Considering the widespread use of glimepiride in managing T2DM, in the present article, the role of glimepiride in controlling hyperglycemia and its place in the T2D management landscape is reviewed. The efficacy and safety, adverse effects (hypoglycemia and weight change), and affordability and patient compliance associated with diabetes are also discussed.

Methods

The authors conducted a systematic review of published literature to evaluate the place of glimepiride in the evolving landscape ofT2D management.

Literature Search

The search was primarily conducted on Medline, PubMed and Google Scholar. The aim of the authors was to evaluate all the published literature including randomized clinical trials, clinical trials, retrospective and prospective research, systematic reviews, and meta-analysis for glimepiride in T2D management and its CV safety. A search was conducted on the digital bibliographic database, Medline, PubMed, Google Scholar. The MeSH terms and search phrase used were (((Glimepiride) AND (Type 2 Diabetes Mellitus)). Two important papers were identified on glimepiride and T2DM. In a backward chronological search, all the relevant articles were searched for citations. Titles and abstracts following the electronic search were examined, and full-text articles fulfilling the selection criteria were obtained. Full text of the selected articles was thoroughly screened to extract the study data.

Screening

Titles and abstracts from the electronic search were checked, and articles meeting the selection criteria were obtained. Relevant information from all the selected articles was extracted. Two investigators independently extracted data from selected literature, and any difference of opinion was resolved through deliberations and consensus between the authors. Where an agreement was not reached, a third author acted as the referee. Qualitative analysis of the selected articles was then conducted by the investigators.

Data Items, Extraction and Synthesis

The study data were extracted by reading the complete article. Selected articles were reported in a table comprising of the following fields: record number, the name of the author(s), publication year, article title and journal. Relevant data for eligible articles were extracted by two authors using pre-structured data extraction grids. These grids were used to extract author name, year of reporting, geographic area, use of glimepiride, benefits, clinical trials, CV safety and adverse events associated with using glimepiride. The disagreements were resolved as detailed above.

Data Synthesis and Analysis

The authors have presented the results in narrative summaries. The themes that emerged after a thorough assessment of the selected articles comprised of the place of glimepiride in T2D management, its glycemic potency, efficacy, durability, CV safety concerns, cost-effectiveness and compliance.

The Changing Landscape of T2DM Management

The management of T2DM is marked with the increasing complexity of management, raising concerns over safety and cost of therapy. In India, the average number of antidiabetic drugs per prescription is 1.4, and the mean cost per 1-month prescription is INR 354.60 ± 305.72.[4,5] The introduction of newer antidiabetic drugs has transformed the prescription pattern across the globe. While oral hypoglycemic agents (OHAs) constitute 57% of the prescribing patterns, insulin alone makes up 14% and OHA + insulin combination about 13% of the prescription pattern. Similar trends are seen in South Asia, where a majority of the treatment pattern is constituted by OHA, either as monotherapy or in combinations. An ideal antidiabetic drug should offer glycemic control, with reduced risk of side effects, while providing economic ease of use.[6]

In the course of T2D management, a gradual reduction in the functional β-cells leads to continuing the decrease in the glucose-lowering efficacy of OADs over time. In consideration of this early combination therapy with intensive glycemic control may be an effective approach for better preservation of β-cell function,

which may rapidly achieve the goal of glycemic level and reduce the diabetes-related complications. An early initiation of combination therapy also brings down complications, which may occur due to up-titration of monotherapies. It has been now established that if the initiation of combination therapy is delayed in stepping up from monotherapy, an increased risk of long terms of hyperglycemia and micro- and macrovascular complications may occur.[3]

Place of Glimepiride in T2D Management Therapy

The antihyperglycemic action of metformin occurs independently without affecting the insulin secretion. Hence, it is beneficial when metformin is combined with an insulin secretagog, like an SU. Modern SUs like glimepiride are considered an ideal choice due to their high efficacy, relative CV safety and low-cost. The risk of hypoglycemia and weight gain can be reduced using modern SUs such as glimepiride and gliclazide with lesser side effects and better efficacy. These effects can be attributed to the wider use of modern SUs. In addition, combination therapies also lead to a higher reduction in blood glucose-lowering effect compared with monotherapy.[3] In addition to lowering the glucose by increasing insulin release from the pancreatic β-cells, glimepiride lowers the risk of hypoglycemia among SUs. Glimepiride can be safely used in patients with CV risk, cardiovascular disease (CVD) and in younger patients with diabetes.[7]

The availability of modern SUs like glimepiride with lesser side effects and improved efficacy has made them a popular antidiabetic option. Owing to its efficacy, cost and feasibility, glimepiride is one of the drugs which are most widely prescribed across the globe.[8] However, there are concerns about CV safety, hypoglycemia and weight gain associated with its use.

Since glimepiride is CV neutral as compared to other SUs, the degree of inhibition of K_{ATP} channels in T2DM patients is less severe during treatment with glimepiride. Hence, it can be safely used in T2DM patients with concurrent coronary artery disease.[9,10]

The low frequency of hypoglycemia and weight gain offered by modern SUs as compared with conventional SUs may be attributed to its reduced binding affinity (2- to 3-fold) and rapid association and dissociation with SU receptors. According to an International Task Force, glimepiride like modern SUs should be preferably used in individuals who are overweight/obese withT2DM, at high risk of hypoglycemia or high risk of CVDs. The main objective of using modern SUs, especially glimepiride and gliclazide is to reduce mortality, achieve better outcomes and preserve renal functions.[11] Along with glycemic control, glimepiride also causes many extra-pancreatic effects which contribute to a better outcome with glimepiride in T2DM patients.[12] Table 1 shows the available strengths of glimepiride as monotherapy and as fixed-dose combinations.

A consensus statement by an initiative of the South Asian Federation of Endocrine Societies (SAFES) has recommended that:[12]

- Glimepiride should be started early in the management of T2DM so that maximum benefits can be attained, and benefits of metabolic memory can be achieved.
- Combination of glimepiride in dual or triple fixed drug combinations with drugs that may have complementary modes of action is beneficial in reducing the cost, offering convenience and in improving patient adherence.
- Glimepiride or gliclazide are preferred over conventional SUs given their reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction [MI], stroke and CV mortality) and renal protection.
- Also, glimepiride and gliclazide MR are recommended to be preferred over conventional SU in patients at increased risk of hypoglycemia, overweight/obese and an increased risk of CVD.
- Glimepiride and gliclazide MR are also recommended in elderly patients because of their lower risk of hypoglycemia.

Glycemic, Efficacy and Durability

Modern SU such as glimepiride exhibit certain pleiotropic effects such as insulin clearance, glucagon secretion, insulin sensitization and antioxidative effect, which may have better effect glycemic durability compared to conventional SU.[11]

Glimepiride as monotherapy is a very effective antidiabetic agent. It was shown in a trial by Goldberg et al that 4-mg dose provided a nearly maximal antihyperglycemic effect. All glimepiride regimen significantly reduced fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) values ($p < 0.001$) compared to placebo by the end of the study period.[13] Another study showed equal effects on FPG, PPG, HbA1c, C-peptide and insulin levels in a crossover study of 98 patients treated with glimepiride.[14] Glimepiride monotherapy

Table 1. Available Strengths of Glimepiride as Monotherapy and as Fixed-dose with Other OADs.[12]

Available strengths (mg)	Dose recommendation	Dose titration
Monotherapy		
0.5, 1, 2, 3, 4, 6	With breakfast or the first main meal Adult:1-2 mg daily Geriatric:1 mg daily	Adult:1-2 mg every 1-2 weeks as needed Geriatric & renal: Conservative titration
FDC: Glimepiride + metformin		
0.5/500, 1/500, 2/500, 1/850, 2/850, 3/850, 1/1000, 2/1000, 4/1000	With meals	As with individual agents
FDC: Glimepiride + pioglitazone		
1/15, 2/15, 2/30, 4/30, 4/45	With the first main meal Initial dose: 2-4/30 mg OD	As with individual agents
FDC: Glimepiride + metformin + pioglitazone		
1/500/15, 2/500/15	Once or twice a day as per recommendation	As with individual agents
FDC: Glimepiride + metformin + voglibose		
1/500/0.2, 2/500/0.2, 1/500/0.3, 2/500/0.3	1/500/0.2 mg OD 2/500/0.3 mg OD or BID 2/500/0.3 mg BID	As with individual agents

reduced both FPG and PPG levels more than placebo once daily administration is equivalent to twice daily dosing. Studies have suggested that glimepiride controls blood glucose level throughout the day via its effect on stimulating insulin release, which appears to be more than 2 hours after meals than under fasting conditions. The trial findings have shown that glimepiride enhances insulin and C-peptide secretion under physiologic conditions.[15]

In a randomized, open-label, parallel study including 34 patients with T2DM treated with metformin with an HbA1c of 7.0% to 10.0%, it was seen that similar significant improvements in HbA1c levels were seen in both vildagliptin (-0.8%) and glimepiride (-0.9%). However, the mean amplitude of glycemic excursions (MAGE) and the mean of daily differences (MODD) was significantly reduced by vildagliptin ($p = 0.044$ and $p = 0.031$, respectively) but not by glimepiride. The result of the study has shown that vildagliptin effectively improved glucose level with a considerably higher reduction in glycemic variability and hypoglycemia than glimepiride in patients with T2DM ongoing metformin therapy.[16]A randomized, multicentric, two arms, open study comparing the glycemic efficacy of sitagliptin with glimepiride showed them to be equally effective in controlling HbA1c. The results showed that glimepiride and sitagliptin were equally effective in glycemic control and all other parameters; however, the only difference being the higher and statistically significant frequency of hypoglycemic events in the glimepiride group. Glimepiride and sitagliptin have shown equal efficacy in glycemic control and all other related parameters. The only difference was reported in terms of hypoglycemic events, which was reported to be higher and statistically significant in the glimepiride group.[17]

In an open-label, randomized, comparative, multicenter study, the safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with T2DM was evaluated. The results have shown that in patients with T2DM, glimepiride/metformin combination demonstrated exhibited significant reduction in glycemic parameters compared with sitagliptin/metformin combination. In addition, there was no considerable change in both the groups in terms of alterations in body mass index (BMI) and hypoglycemic incidence. The results showed that after 12 weeks of treatment, there was a statistically

significant difference in the mean HbA1c decrease in glimepiride group (0.42%) compared with sitagliptin group (0.30%) (p = 0.001). Mean decrease in FPG and PPG was also considerably lower in the glimepiride group as compared to the sitagliptin group (p = 0.008).[18]

It was reported that when used in combination with vildagliptin, glimepiride was effective in Chinese patients with T2DM minus raising the risk of hypoglycemia and weight gain. In a 24-week randomized double-blind placebo-controlled study, it was seen after 24 weeks treatment with vildagliptin 50 mg, OD and glimepiride daily dose 3.3 mg; the adjusted mean change in HbA1c was -0.7% (-8 mmol/mol; baseline 8.6%, 70 mmol/mol) in the vildagliptin group and -0.2% (-2 mmol/mol; baseline 8.7%, 72 mmol/mol) in the placebo group, with a treatment difference of -0.5% (-5 mmol/mol; p <0.001). A slight, but not significant, reduction in body weight was seen in both groups.[19]

A study conducted in Japanese subjects showed that the combination therapy with sitagliptin and low-dose glimepiride (0.5 mg/day) is effective as well as safe in individuals who had T2D uncontrolled with high-dose glimepiride. Even though the dose of glimepiride was reduced, combination therapy with sitagliptin induced significant improvements in HbA1c levels (-0.8%, p <0.001).[20] An 18-week randomized parallel-group interventional trial showed that the addition of sitagliptin and glimepiride to metformin monotherapy brought about significant improvement in glycemic control. Benefits were more with glimepiride contrary to sitagliptin. The results showed that at 18 weeks both sitagliptin and glimepiride produced significant (p <0.001) reduction in HbA1c (-0.636% and -1.172%, respectively), with 12% patients in sitagliptin group and36% patients in glimepiride group achieving target HbA1c. The reduction was significant (p <0.001) in both group in FPG (-15.49 mg and -29.84 mg, respectively) and 2-hour PPG (-34.28 mg and -44.83 mg, respectively).[21]

The results of a systematic review conducted by Amate et al showed that a greater effectiveness was observed in the glimepiride/metformin combination, despite slight differences in adverse effects, with absence of severe hypoglycemia in more than 98% of patients being treated. The glimepiride/metformin combination was preferred treatment due to the cost as well as the effectiveness and safety. The study authors concluded that glimepiride offers potential benefit in refractory hyperglycemic populations, tolerant to treatment.[22]

The ability of glimepiride to increase first- and second-phase insulin secretion in T2DM patients are reflective of a possible association between reasonable glycemic control and acute improvement of control of the *in vivo* insulin release process.[23]

Safety of Glimepiride

Hypoglycemia

Earlier, it has been postulated that glimepiride, which is a long-acting SU, may heighten the risk of hypoglycemia when compared with the short-acting drugs.[24] An observational study has shown that long-acting SUs were associated with an increased risk of severe hypoglycemia compared with the use of specific, short-acting SUs. However, a secondary analysis showed no significant differences in the risks profile.[25] Another Clinical Practice Research Datalink (CPRD)-based study also reported no difference in hypoglycemic risk between long-acting and short-acting SUs.[24,26] It has also been established that the increased risk of hypoglycemia does not apply to every stage of diabetic disease.[24] It has been proven that while longer-acting SUs led to an almost threefold higher incidence of severe hypoglycemia compared with shorter-acting SUs when used as the first-line treatment,[26] but the incidence of severe hypoglycemia in the two groups was similar when the drug was given as a second-line treatment.[27]

Glimepiride has been compared with other SUs, including glibenclamide, glipizide and gliclazide in many clinical trials. The incidence of hypoglycemia was lower with glimepiride (1.7%) than with glibenclamide. Another study showed glimepiride to be associated with fewer hypoglycemic episodes compared to glibenclamide.[15] When compared with gliclazide, the use of glimepiride was associated with a similar incidence of hypoglycemic episodes. The study concluded that glimepiride is as effective as gliclazide either as monotherapy or in combination therapy.[28]

Weight Gain

Sulfonylureas have been linked with considerable weight gain, a secondary side effect which is also known to be associated with the use of insulin, thiazolidinediones and glinides. Glimepiride has reported weight neutrality at least for the first year of use.[29] Glimepiride administered once daily was linked with weight neutralizing or weight-reducing effect over 1.5 years. Another study showed that once-daily

glimepiride provides effective glycemic control and may be beneficial over other SUs as it shows weight neutralizing/reducing effects in patients with T2D. In an open, uncontrolled surveillance study, it was seen that treatment with glimepiride led to significant and stable weight loss relative to baseline except for patients with a BMI of <25 kg/m^2. Mean body weight was lowered from 79.8 kg at baseline to 77.9 kg after 4 months, 77.2 kg after 1year and 76.9 kg after 1.5 years (mean intra-individual change from baseline: -1.9 kg, p <0.0001; -2.9 kg, p <0.05, respectively).[30]

Initial treatment with glimepiride led to a significantly higher reduction in body weight or BMI than with glibenclamide (-2.04 ± 3.99 kg vs. -0.58 ± 3.65 kg, p <0.001; -0.71 ± 1.38 kg/m^2 vs. -0.20 ± 1.28 kg/m^2, p <0.001, respectively), while providing equivalent glycemic control.[31]

Cardiovascular Safety Concerns

Glimepiride is a pancreas nonspecific SU which is also known to bind to cardiac muscle and vascular smooth muscle cells, and hence there have been concerns regarding its raised CV risks.[32,33] However, animal studies have demonstrated that glimepiride upon binding to the myocardium could preserve or even show some ischemic preconditioning, eventually preventing ventricular arrhythmias.[34]

It has been seen that modern SUs are linked with reduced risk of CV mortality, MI and hospitalization for acute coronary syndrome (ACS) when compared with traditional SUs.[35] The major adverse CV event (MACE) outcome safety data for glimepiride is reassuring and preliminary research in the field of personalized medicine as shown that drugs directly targeting β-cell insulin exocytosis may continue playing an essential role in managing T2D.[36] Simpson et al in 2015 showed in a meta-analysis of 18 studies, including 1,67,327 patients that gliclazide and glimepiride were linked with reduced risk of all-cause and CV mortality compared with glibenclamide. Trials have shown that the risk of all-cause and CV mortality was lesser with glimepiride and gliclazide compared with glibenclamide (all-cause mortality for gliclazide 0.65, 955 confidence interval [CI] 0.53-0.79).[37]

In a review by Aravind et al have shown that several clinical studies have validated the 'cardio-safe' profile of glimepiride; hence, making it suitable for use in a wide range of people with diabetes. Compared with other conventional SUs, glimepiride is cardio-safe. It has been reported to have an insignificant effect in reducing coronary blood flow and in increasing coronary resistance. Glimepiride preserves ischemic preconditioning since it does not have such inhibitory effects, hence preferred over conventional SUs, particularly in patients at increased risk for CVD.[38]

In a cohort study using real-world data, the results have shown that for patients with diabetes taking an insulin secretagogue, glimepiride was related with the best clinical outcome, exhibiting the lowest mortality and CV event risk. The results showed that among glimepiride, gliclazide, glipizide, glyburide and repaglinide groups, glimepiride was associated with the best clinical outcome, exhibiting lowest mortality and CV event risk of the five insulin secretagogues. In the study results revealed that the adjusted HR of all-cause mortality and CV event risk were 1.52 (p <0.001) and 1.22 (p = 0.005) for gliclazide, 1.42 (p <0.001) and 1.19 (p = 0.073) for glipizide, 1.43 (p <0.001) and 1.32 (p <0.001) for glyburide, and 1.88 (p <0.001) and 1.69 (p = 0.001) for repaglinide.[39]

In a study by Douros et al, it was seen that when compared with other second-generation SUs, glimepiride was linked with a similar incidence of MI and ischemic stroke, with a nonsignificant trend towards an increased incidence of severe hypoglycemia. On the contrary, glimepiride use was associated with a reduced incidence of all-cause mortality, and a nonsignificant trend of a lower incidence of CV death. During a mean follow-up of 1.1 years, SUs were related with an increased risk of MI (incidence rate 7.8 vs. 6.2 per 1,000 person years, HR 1.26, 95% CI 1.01-1.56), all-cause mortality (27.3 vs. 21.5, 1.28, 1.15-1.44) and severe hypoglycemia (5.5 vs. 0.7, 7.60, 4.64-12.44) compared with continuing metformin monotherapy. A trend towards increased risks of ischemic stroke (6.7 vs. 5.5, 1.24, 0.99-1.56) and CV death (9.4 vs. 8.1, 1.18, 0.98-1.43).[26] The findings from the CAROLINA trial showed that there is no difference in the risk of CV events or all-cause mortality between the dipeptidyl peptidase-4 (DPP-4) inhibitors linagliptin and glimepiride. The findings revealed that the primary outcome occurred in 356 of 3,023 participants (11.8%) in the linagliptin group and 362 of 3,010 (12.0%) in the glimepiride group (hazard ratio [HR], 0.98 [95.47% CI, 0.84-1.14]; p <0.001 for noninferiority), meeting the noninferiority criterion but not superiority (p = 0.76). Adverse events occurred in 2,822 participants (93.4%) in the linagliptin group and 2,856 (94.9%) in the glimepiride group, with 15 participants (0.5%) in the linagliptin group vs. 16 (0.5%) in the glimepiride group with adjudicated-confirmed acute pancreatitis.[40]

The TOSCA.IT, a multicenter, randomized, pragmatic clinical trial, including patients aged 50 to 75 years with T2D with uncontrolled blood glucose with metformin monotherapy. A comparison of glimepiride, gliclazide and pioglitazone showed that the primary outcome (a composite of the first incidence of all-cause death, nonfatal MI, nonfatal stroke or urgent coronary revascularization) occurred in 105 patients (1.5 per 100 person-years) who were given pioglitazone and 108 (1.5 per 100 person-years) who were given SUs (HR 0.96, 95% CI 0.74-1.26, p = 0.79). The trial authors concluded that the incidence of CV events was similar with glimepiride, gliclazide and pioglitazone as add-on treatments to metformin and hence are suitable options in terms of efficacy and adverse events in the management of diabetes.[41]

In an observational study which evaluated the correlation between selectivity for β-cells among several SUs and CV mortality among T2DM patients, the patients treated with a combination of SUs and biguanides at enrollment had considerably higher mortality when compared with the rest of the sample (5.2% vs. 6.4% annually; p <0.05). Compared with glimepiride, mortality was significantly higher in patients treated with repaglinide and gliclazide. The study authors concluded that glimepiride due to its higher selectivity for β-cells was associated with reduced mortality when used in combination with metformin, compared with other SUs like glibenclamide.[42]

In a study evaluating the impact of SUs on in-hospital outcome in MI, patients assessed the difference in outcomes between MI patients vs. diabetic patients who did not receive SUs. The findings showed that the incidence of in-hospital complications, mainly, in-hospital death was more in the insulin group compared with the glimepiride or gliclazide group.

This study concluded that the hospital mortality among patients admitted with acute MI and who received glimepiride or gliclazide before admission was comparatively lower than that among patients who did not receive similar treatments.[43] Another study which compared the association between the choice of SU and the risk of overall mortality among a large cohort of patients with T2D with coronary artery disease (CAD) demonstrated a trend towards increased overall mortality risk with glyburide vs. glimepiride (1.36 [0.95-1.91]) and glipizide vs. glimepiride (1.39 [0.99-1.96]). The study suggested that glimepiride may be the preferred choice of SU in individuals with underlying CAD.[44]

Cost-Effectiveness and Compliance

Diabetes is a complex disease; pharmacotherapy for a chronic disease like diabetes has substantial economic implications for patients especially in a developing nation like India. In terms of cost-effectiveness, only efficacy may not justify a drug choice for long-term therapy as the occurrence of adverse events such as β-cell loss, hypoglycemia, negative CV effects. Management of adverse effects such as hypoglycemia poses an additional health and economic burden on the public.[45,46]

As is seen from the ensuing discussion that modern SUs like glimepiride have a lower risk of hypoglycemia and have favorable cost, efficacy and safety profiles. Sulfonylureas as a class of antidiabetic medicines form a reasonable choice for diabetes management, especially when the cost is a crucial consideration. The risk of hypoglycemia linked with glimepiride can be easily tackled with the help of patient education and the use of variable dosing. Glimepiride is one of those modern SUs which have a lower risk of hypoglycemia compared with conventional SUs.[11]

In a review, the authors concluded that metformin, glimepiride and pioglitazone are safe and efficacious oral hypoglycemic medicines. Glimepiride is the preferred SU as it is not associated with the adverse events as others in its class. Glimepiride was not associated with weight gain, hypoglycemia or negative CV events relative to other SUs.[45]

A study conducted to evaluate the cost-effectiveness of commonly practiced combination therapies in the management of T2DM. The cost-effectiveness for per unit reduction in HbA1c and FPG was significant in metformin *plus* glimepiride group as compared to the metformin *plus* teneligliptin group though it was comparable for both the groups for per unit PPG reduction. However, there was no significant change in BMI levels between the groups. The authors concluded that compared to combination of metformin with teneligliptin, the metformin-glimepiride combination is a significantly cost-effective therapy when used as an initial combination therapy in patients of T2DM in reducing HbA1c and FPG.[46]

In the case of Asian diabetic patients, an open, randomized, comparative, multicenter, clinical trial to assess the efficacy and safety glimepiride was conducted. The results showed that the frequency of successful blood glucose control (3.9 < FBG <7.8 mmol/L) was not considerably different from other groups. The authors suggested that glimepiride could be used

effectively and safely for the control of hyperglycemia; however, since glimepiride demonstrated equivalent efficacy with a single dose, it was anticipated that it might improve patients' compliance.[15]

Given this, treatment with modern SUs like glimepiride is associated with reduced economic load and better performance in terms of the outcome when compared with other regimens in the cost for average glycemic-lowering. Also, the once-daily dosing schedule via the oral route of administration is an essential feature of glimepiride, making it an appropriate option for improved adherence to medication regimen.[12]

Conclusion

Optimized glycemic control, reduced risk of side effects, along with economic feasibility, are the main features of oral antidiabetic agents. Glimepiride is a modern SU which is CV neutral as compared to other SUs and hence can be safely employed in managing T2DM. Multiple studies have reported glimepiride to be safe for use in people with T2D at increased CV risk. It is recommended to be initiated early in the management of T2DM for attaining maximum benefits. Patient compliance and affordability associated with glimepiride make it an attractive option in the management of T2DM.

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CASE REPORT

Lingual Thyroid: A Case Report

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ABSTRACT

Lingual thyroid is a rare developmental anomaly caused due to the aberrant embryogenesis during descent of the thyroid gland from the foramen cecum to its pre-laryngeal site. Foreign body sensation in throat, dysphagia, dysphonia, pain and bleeding are the common presenting symptoms of this condition. Treatment includes the use of exogenous thyroid hormone to correct the hypothyroidism and to induce the shrinkage of the gland. Other treatment options include surgery and radiotherapy when symptoms of obstruction, bleeding and malignant transformation are present. Presented here is the case of a 39-year-old male presenting with foreign body sensation in throat of 1 week's duration. The patient was diagnosed with lingual thyroid. Treatment with 50 µg/day of L-thyroxine was advised and surgery was deferred as the patient was asymptomatic.

Keywords: Lingual thyroid, ectopic thyroid, technetium-99m thyroid scan, L-thyroxine

Introduction

Lingual thyroid is a rare developmental anomaly caused due to the aberrant embryogenesis during descent of the thyroid gland to the neck. The first case of lingual thyroid was reported in 1869 by Hickman. Most frequent ectopic location (about 90%) of the thyroid gland is in the base of the tongue. Other sites include sublingual, thyroglossal and laryngotracheal, mediastinal and esophageal. Prevalence rate ranges from 1 in 1,00,000 to 1 in 3,00,000 population; 0.3% of cases will present in hypothyroid state. Diagnosis is mainly by clinical suspicion and confirmation by imaging.

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Case Report

A 39-year-old male presented with foreign body sensation in throat of 1 week's duration. There was no history of dysphagia, nocturnal dyspnea and sleep apnea/dysphonia. There were no signs of thyroid dysfunction. On intraoral examination, a globular lesion popped up near the mid-line of base of tongue on gagging (Fig. 1).

On videolaryngoscopy examination, a globular swelling measuring about 2.5 cm in diameter, smooth surfaced, extending from dorsal surface of base of tongue to lingual surface of epiglottis was noted. On palpation, the swelling was hard in consistency without any pain or discomfort. No bleeding points were seen. Ear, nose and neck examination was normal. Provisional diagnosis of lingual thyroid was made based on its location and appearance. The patient was advised for following investigations:

- Thyroid function test results showed the following parameters:
  - Triiodothyronine (T3) - 1.22 ng/mL, thyroxine (T4) - 6.24 ng/mL and thyroid-stimulating hormone (TSH) - 14.29 mIU/mL

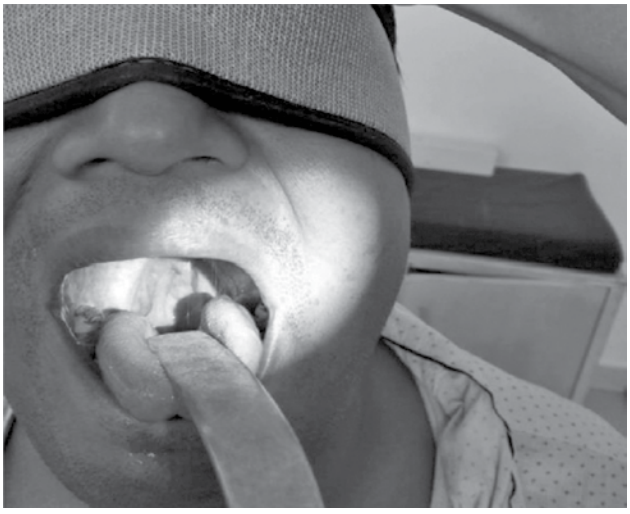

Figure 1. Intraoral examination.

- T3 and T4 were measured by competitive electrochemiluminescent immunoassay
- TSH by sandwich electrochemiluminescent immunoassay.

- Ultrasonography of neck showed absent thyroid gland in thyroid fossa. Heterogeneous echo pattern solid lesion in the base of the tongue on the right side suggested lingual thyroid.
- Radionuclide thyroid scan and uptake study using 3 mCi of technetium-99m pertechnetate was done, which revealed abnormal radiotracer concentration in the base of tongue consistent with ectopic thyroid tissue. Thyroid gland was not visualized in its normal position. Thus, it indicated that this lingual thyroid is the only functioning thyroid gland.

The patient was advised 50 µg/day of L-thyroxine and surgery was deferred as the patient was asymptomatic.

Discussion

Lingual thyroid is the presence of ectopic thyroid tissue anywhere between circumvallate papillae of the tongue to epiglottis along the primitive thyroglossal duct. This is due to the embryonic failure of descent of normal thyroid tissue from foramen cecum area of base of tongue to the lower part of the neck in front of the thyroid cartilage. It has been hypothesized that the cause for the arrest in descent of thyroid anlage is due to the maternal antibodies against thyroid antigen.

The incidence of lingual thyroid is reported as 1 in 1,00,000. It is seven times higher in females when compared to males. About 33-62% of all patients have hypothyroidism with elevated levels of TSH.

Foreign body sensation in throat, dysphagia, dysphonia, pain and bleeding are the common presenting symptoms of this condition.

Investigation for lingual thyroid includes serum thyroid profile, radionuclide technetium-99m and iodine-131 thyroid scans. Other investigations include computed tomography (CT) and magnetic resonance imaging (MRI) of the neck with contrast, which helps in planning treatment. In our case, same radionuclide technetium-99m scan was done and abnormal radiotracer concentration in the base of the tongue was noted, consistent with ectopic thyroid tissue. Thyroid gland was not visualized in its normal position.

The treatment options that are available for lingual thyroid include surgery, radioiodine ablation and chemotherapy. The choice of treatment depends on symptoms such as dysphagia, sleep apnea, bleeding from the lesion, location and extent of the lesion.

Treatment of an asymptomatic patient in euthyroid state is regular follow-up. In hypothyroid patients, L-thyroxine is supplemented for suppressing the TSH levels as well as to reduce the size of the lesion. Indications for surgery include severe obstructive symptoms and complications such as bleeding, cystic degeneration or malignancy. Surgical excision may be considered after confirmation of adequate thyroid tissue in the neck by radioisotope scan. Surgical excision can be done either transorally or externally through a transhyoidal pharyngotomy. In patients lacking thyroid tissue in the neck, the lingual thyroid can be excised and implanted in the muscles of the neck.

In the present case, the patient was kept on hormone replacement therapy with L-thyroxine and was followed-up regularly every 3 months. Surgical excision was not considered in the present case as it was the only functioning thyroid gland. However, surgical excision can be considered in future, if malignant transformation occurs.

Conclusion

When a mass is observed in the base of tongue, ectopic lingual thyroid must be kept in mind for differential diagnosis. The diagnosis can be confirmed using ultrasonography, radionuclide thyroid scan, CT and MRI scans. Treatment option is based on symptomatology.

Suggested Reading

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News and Views

Maternal Graves's Disease and Neonatal Hypothyroidism

Neonates born to mothers with Graves' disease (GD) were at high risk of neonatal hypothyroidism if their mothers had high serum free thyroxine (fT4) and thyrotropin receptor autoantibodies (TRab) levels in the third trimester compared to mothers who delivered euthyroid newborns, says a new research published in the journal *Thyroid*.[1]

Researchers enrolled 305 pregnant women with Graves' disease who delivered at a hospital in Tokyo between August 2005 and May 2022. Of these, 242 women were treated with propylthiouracil (PTU) and 63 received methimazole. Umbilical cord thyroid stimulating hormone (TSH), fT4 and TRAb levels were measured at delivery. Maternal thyroid profile (free T4, TSH receptor antibodies) and daily antithyroid drug doses were assessed all through the pregnancy and at delivery. Data for the study was obtained from the hospital medical records of the participants. Through this study, the researchers aimed to determine if neonatal hypothyroidism at delivery and maternal fT4 levels, TRAb levels, and daily ATD doses during pregnancy were correlated.

The rates of neonatal hypothyroidism at delivery, which was the primary study objective, were comparable between the two groups. Nearly 13% infants born to mothers taking PTU had neonatal hypothyroidism; among infants born to mothers on methimazole, the incidence was 19%. In the PTU group, one newborn had neonatal goiter and two needed levothyroxine treatment.

The daily dose of the antithyroid drug was found to have the strongest association with neonatal hypothyroidism at delivery, the cut-off dose predictive of neonatal hypothyroidism was 150 mg/day for PTU and 10 mg/day for methimazole.

The cut-off dose of antithyroid drugs for neonatal hypothyroidism risk were determined, based on maternal TRAb levels. The cut-off PTU dose remained the same at 150 mg/day when the TRAb level was >3 times the upper limit of the normal during the third trimester, the cut-off dose increased to 20 mg/day for methimazole.

Compared to women on methimazole who delivered euthyroid newborns, those who delivered newborns with hypothyroidism were on higher doses of methimazole at 20-28 weeks of gestation (17.5 mg/day vs 10 mg/day) and 28-36 weeks (15 mg/day vs 5 mg/day). They also had lower free T4 levels at delivery (0.93 ng/dL vs 1.4 ng/dL). Similarly, in the PTU group, women with hypothyroid newborns were on higher PTU doses at 20-28 weeks of gestation (200 mg/day vs 75 mg/day) and 28-36 weeks of gestation (200 mg/day vs 50 mg/day). However, their TRab (6.1 IU/L vs 3 IU/L) and free T4 (1.48 ng/dL vs 1.12 ng/dL) levels were higher.

With each 5 mg increase in the dose of methimazole at 28 to 36 weeks of gestation, the likelihood of neonatal hypothyroidism nearly doubled with an odds ratio of 1.9. With each 50 mg increase in the dose of PTU, the probability of neonatal hypothyroidism increased slightly more than 2-folds with OR of 2.3.

This study has for the first time identified factors that were predictive of neonatal hypothyroidism at birth. Mothers with Graves' disease who delivered hypothyroid newborns had high TRab and free T4 levels in the third trimester indicating high maternal disease activity for which they needed high daily doses of antithyroid drugs. Active maternal Graves's disease therefore can be considered as a risk factor for neonatal hypothyroidism. Such women should be carefully monitored all through the pregnancy and at delivery. Measurement of TRAb and free T4 levels in the mothers in the third trimester and cord blood TSH, fT4 and TRAb at delivery may help identify newborns at risk of neonatal hypothyroidism.

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■■■■

Lighter Side of Medicine

HUMOR

But Where Were You Yesterday?

Tom had this problem of getting up late in the morning and was always late for work. His boss was mad at him and threatened to fire him if he didn't do something about it. So, Tom went to his doctor who gave him a pill and told him to take it before he went to bed. Tom slept well, and in fact, beat the alarm in the morning. He had a leisurely breakfast and drove cheerfully to work. "Boss", he said, "The pill actually worked!" "That's all fine" said the boss, "But where were you yesterday?

New Teeth

Our local minister had all of his remaining teeth pulled and new dentures made a few weeks ago.

The first Sunday, his sermon lasted 10 minutes. The second Sunday, he preached only 20 minutes. But, on the third Sunday, he preached for an hour and a half.

I asked him about this. He then told me "well, John, that first Sunday, my gums were so sore it hurt to talk. The second Sunday, my dentures were still hurting a lot. Now the third Sunday, I accidentally grabbed my wife's dentures AND I COULDN'T STOP TALKING!"

My Grades

A high-school student came home one night rather depressed.

"What's the matter, Son?" asked his mother.

"Aw, gee," said the boy, "It's my grades. They're all wet."

"What do you mean 'all wet?'"

"You know," he replied, "…below C-level."

Bank Name

Mother decided that 10-year-old Cathy should get something 'practical' for her birthday. "Suppose we open a savings account for you?" mother suggested. Cathy was delighted. "It's your account, darling," mother said as they arrived at the bank, "so you fill out the application."

Cathy was doing fine until she came to the space for 'Name of your former bank.' After a slight hesitation, she put down 'Piggy.'

Doc says, "Joe, I got some bad news for you. You've got 6 months to live."

Joe says, "Six months? Doc, I can't pay your bill in 6 months, I can't do it!"

Doc says, "OK, I give you a year..."

Patient: "Doctor, I get heartburn every time I eat birthday cake."

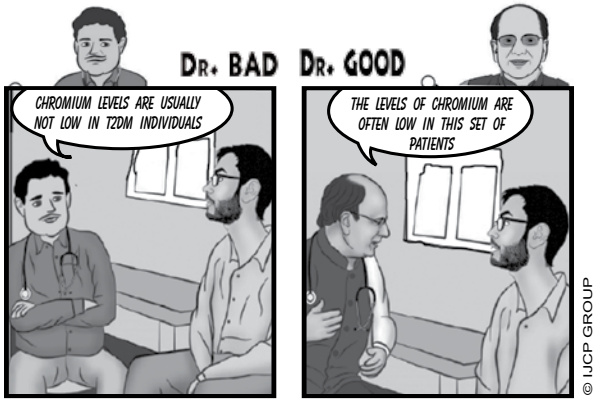
Doctor: "Next time, take off the candles."

When an employment application asks who is to be notified in case of emergency, I always write, "A very good doctor".

My therapist told me that a great way to let go of your anger is to write letters to people you hate and then burn them. I did that and I feel much better but I'm wondering... do I keep the letters?

Dr. Good and Dr. Bad

SITUATION: A 45-year-old type 2 diabetic male had lower plasma chromium levels.



LESSON: According to a case-control study, an inverse association has been demonstrated between plasma chromium levels, T2DM and prediabetes.

Nutrients. 2017;9(3):294

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