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Review Article

Dietary Fiber in the Management of Type 2 Diabetes Mellitus: A Narrative Review

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Abstract

Type 2 diabetes mellitus (T2DM) has become a worldwide epidemic, especially in Asian countries as a result of rapid socioeconomic development, overnutrition, and lack of physical activity. Among the strategies for preventing and managing T2DM, the promotion of healthy dietary habits plays an important role. Various studies which were mainly carried out in Western countries showed that higher dietary fiber (DF) intake has a significant association with a lower risk of the development of T2DM. Thus, a narrative review concentrating on the macronutrient DF was performed. PubMed and Google Scholar were used for this purpose. The goal was to examine the most recent medical research on the advantages of DF for health, with a particular emphasis on how DF consumption affects glycemic management.

Keywords: Diabetes management, diabetes mellitus, dietary fiber, soluble fiber

Introduction

Diabetes mellitus (DM) is a growing worldwide epidemic. Based on the latest statistics reported by the International Diabetes Federation, approximately 537 million adults are affected by this chronic disease.[1] As per current reports, India is considered as the diabetes capital of the world owing to rapidly developing type 2 DM (T2DM) in the country. T2DM is associated with numerous complications, including kidney failure, blindness, increased susceptibility to infection, coronary heart disease, and stroke. It is predicted that by 2030, about 10% of the world's population will have DM.[2] Given the severity of diabetes consequences, early nutrition instruction is essential for prolonging or preventing the disease start. Scientific, clinical, and nutritional experts are aware of the impact of dietary fiber (DF) on function and metabolism. However, due to a lack of research regarding the precise quantity and source of fiber needed to raise their glycemic index (GI), there is controversy surrounding the significance of a high-fiber diet in the management of T2DM.[3,4]

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DOI: 10.4103/cdrp.cdrp_21_22

In this narrative review, we concentrated on the macronutrient DF, which is frequently underestimated in medical nutrition therapy. Our goal was to examine the most recent medical research on the advantages of DF for health, with a particular emphasis on how DF consumption affects glycemic management.

Dietary Fiber, Insulin Resistance and Type 2 Diabetes Mellitus

Dietary Fiber

The edible component of plants that is resistant to digestion and absorption in the small intestine is known as DF. Whole-grain cereals, nuts, fruit, vegetables,

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Submitted: 10-Nov-2022 **Revised:** 25-Jan-2023
Accepted: 04-Feb-2023 **Published:** 07-Jul-2023

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How to cite this article: Dharmatti G, Singh NS, Ghag AA. Dietary fiber in the management of type 2 diabetes mellitus: A narrative review. Chron Diabetes Res Pract 2023;2:84-9.

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Figure 1: Common food sources of dietary fiber

pulses, and legumes are major sources of DF, and they often contain a variety of DF kinds as depicted in Figure 1.

The European Food Safety Authority (EFSA) defines DF as nondigestible carbohydrates plus lignin. EFSA provides a long list of substances that constitute DF, including nonstarch polysaccharides, cellulose, pectins, hydrocolloids, fructooligosaccharides, and resistant starch. The laxative action, cholesterol reduction, and serum glucose reduction are vital physiological effects of these nutrients.[4,5]

The DF content of some commonly consumed food in India is depicted in Table 1 derived from the Indian Food Composition Tables, 2017.[6]

Whole-grain foods typically provide around 12% of the total (primarily insoluble cereal) DF by weight.[7] Fresh fruits and vegetables due to high water concentration provide relatively little fiber when this amount is related to fresh weight. When the amount of fiber/100 kcal is stated, these foods are, on the other hand, comparatively high in fiber. Thus, fruits, leguminous plants, and green vegetables, in addition to cereals, make up an average of 6%–24%, 22%–47%, and 2%–8% of the daily fiber consumption in developed nations.[4,5,8,9]

Insulin Resistance and Type 2 Diabetes Mellitus

Elevated blood glucose levels are dangerous even before the onset of diabetes. The injury occurs when the body is unable to respond to a glucose load with the proper quantity of insulin to mediate glucose absorption. It occurs before the onset of T2DM. Insulin resistance (IR) has been linked to an increased risk of a variety of ailments, including hypertension, coronary heart disease, stroke, and cancer, according to research studies.[10]

Table 1: The dietary fiber content of some commonly consumed foods in India

Food groups	DF per 100 g edible portion
Cereals	Rice (0.2 g), Wheat (1.2 g), Bajra (1.2 g), Jowar (2.7 g), Maize (1.6 g)
Pulses	Bengal gram whole (3.9 g) green gram whole (4.1 g)
Vegetables	Lotus stem dry (25 g), Carrot (4.4 g), Cauliflower (1.2 g)
Fruits	Guava (5.2 g), Dates - fresh (3.7 g)

DF: Dietary fiber

Smoking, physical inactivity, and obesity are all factors that contribute to the development of IR. IR can be caused by a variety of factors, including diet. IR is commonly linked to diets heavy in fat, saturated fat, and/or simple carbohydrates, according to a research study.[11]

Clinical investigations have demonstrated a significant reduction in IR in patients whose diets have been supplemented with fiber and foods high in fiber and therefore such diets are advised for diabetes, as fiber slows down the absorption of carbohydrates, preventing the rise in blood sugar critical threshold. By producing a gelatinous mass that slows down food digestion, DF lowers the GI of meals, especially soluble ones, and attenuates postprandial hyperglycemia.[4,12]

DFs have been shown to affect the onset of T2DM and related T2DM-related complications. Given its capacity to lower total cholesterol levels and hyperglycemia in patients with impaired glucose tolerance and T2DM, increasing DF intake is one of the objectives of nutritional counseling that deserves more attention. Increased fiber consumption has also been demonstrated to improve insulin sensitivity and lower systemic inflammation. According to research studies, high-fiber diets (30 g/day) improved biochemical markers, lessened the severity of T2DM, and lowered the prevalence of risk factors for cardiovascular disease.[2]

Dietary Fiber and Metabolic Health

There are two main types of DF: soluble and insoluble. A brief introduction on the types of DF is depicted in Table 2.

Soluble DF has been reported to reduce the risk of developing diabetes and may have therapeutic effects in patients with T2DM. This was well demonstrated in a study conducted among Chinese patients. The study aimed to investigate the effect of soluble DF on metabolic control in patients with T2DM. 117 patients with T2DM between the age group of 40 and 70 years were assessed. These patients were randomly assigned to one of two groups,

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and intervened with extra soluble DF (10 or 20 g/day), or to a control group (0 g/day) for 1 month. The results of the study suggested that increased and regular consumption of soluble DF led to significant improvements in blood glucose levels, IR, and metabolic profiles, without improving the secretory function of the islets of Langerhans, over a short-term intervention period in patients with T2DM.[2]

Consumption of high-soluble DF appears to provide extra metabolic benefits, such as enhanced carbohydrate-rich meal GI and lipid profiles. The release of numerous gut hormones are some of the other impacts of DF that may have an impact on overall metabolic health. DF appears to be associated with improvements in insulin sensitivity and overall metabolic state, according to existing scientific evidence from prospectively designed and controlled research.[13]

Methodology

A narrative review was performed of the current literature. PubMed and Google Scholar were used for this purpose. The search terms were Diabetes mellitus, dietary fiber, soluble fiber, diabetes management, and the role of dietary fiber in diabetes management. We identified 8,650,727 articles by literature search (8,580,000 were identified from PubMed and 70,727 from Google Scholar). We excluded duplicated articles, not relevant articles, and articles with only abstracts and titles. We reviewed all potential and relevant articles with no restrictions on the date of publication.

Table 2: Types of fiber

Soluble fiber	Insoluble fiber
This type dissolves in water and forms a gel-like substance in stomach, slowing down digestion. It helps to control blood sugar and cholesterol, which can help prevent or manage diabetes complications.	This type does not dissolve in water and typically remains whole as it passes through stomach. It supports insulin sensitivity and adds bulk to the stool and appears to help food pass more quickly through the stomach and intestine.
Examples: Apples, bananas, oats, peas, beans, sprouts, and avocados.	Examples: Whole wheat flour, bran, nuts, seeds, and the skins of many fruits and vegetables.[1]

Results and Discussion

A substantial number of clinical trials have been conducted to study the effect of DF intake on the glycemic profile of the patient with diabetes. Some studies reporting the benefits of DFs on glycemic control are depicted in Table 3.[4] The major finding of these clinical trials has reported positive benefits on blood glucose response (decreased fasting plasma glucose level, postprandial glucose, and hemoglobin A1C [HbA_1C]) even with moderate administration of DF in human subjects. Two of the randomized trials also demonstrated positive changes in lipid profile along with glycemic control on the administration of DF, thus supporting the recommendation to increase DF intake.[15,16]

Dietary Fiber Intake and Risk of Developing Type 2 Diabetes

Results from large prospective cohort studies indicate that a high intake of insoluble cereal fibers (in most studies, >30 g/day) or whole-grain products (in most studies, >30–40 g/day) rich in cereal fibers may reduce IR and the risk of developing T2DM by 20%–30%.[6] These

Table 3: Studies on the benefit of fiber intake and its response to glycemic profile in the body

Type of study	Inclusion criteria	Duration	Type and dose of fiber administered	Major findings	References
Randomized, single-blind, controlled, crossover intervention trial	Impaired glucose tolerance	18 weeks	15 g arabinoxylan/day	Improved fasting serum glucose	[14]
Randomized, single-blind, controlled, crossover intervention trial	Healthy and glucose-intolerant subjects	1 year	6 g of fiber, partially hydrolyzed guar gum with each meal	Reduced postprandial plasma glucose, postprandial insulin, triacylglycerol levels	[15]
Randomized, crossover study	Patients with T2DM	6 weeks	Moderate fiber diet (total, 24 g; 8 g of soluble fiber and 16 g of insoluble fiber) and high-fiber diet (total, 50 g; 25 g of soluble fiber and 25 g of insoluble fiber)	Improved glycemic control, decreased hyperinsulinemia, and lowered plasma lipid concentrations	[16]
Randomized double-blind trial	Patients with T2DM between the age group of 40 and 70 years	1 month	Control group; 10 g/day soluble fiber group; 20 g/day soluble fiber group	Significant improvements in blood glucose levels, insulin resistance, and metabolic profile	[2]
Randomized controlled trial	Healthy subjects; T2DM and prediabetic subjects	16 weeks	10 g/day gum Arabic	Decrease fasting blood glucose, health improvement	[17]

DM: Diabetes mellitus, T2DM: Type 2 DM

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findings can be supported by a recent epidemiological study in China among 3250 participants that investigated the relationship between DF intake and newly diagnosed T2DM in a middle-aged Chinese population. As per findings from the study, it was concluded that a higher intake of DF was associated with a decreased risk of newly diagnosed T2DM in a middle-aged Chinese population.[18]

An observation was noted in a recent study among the Japanese population (n = 280) where individuals with higher total DF intake had a lower risk of T2DM. Furthermore, both the soluble and insoluble DF intakes were inversely associated with the risk of T2DM.[14] Thus, the intake of high-DF foods might be an effective approach for diabetes prevention and glycemic control among newly diagnosed T2DM patients.[18,19]

Role of Fiber in Body Weight

Excessive energy consumption leads to obesity, and IR has been identified as the most powerful single predictor of T2DM. As a result, any dietary change that leads to even minor weight loss should reduce IR. However, in obese people, energy expenditure decreases as soon as body weight decreases, and powerful hypothalamus hormonal responses are triggered to prevent further weight loss. Additionally, the majority of people who follow weight loss programs are overweight or obese and often sedentary, making significant gains in lean mass difficult. Physical activity can reduce IR for 2–72 hours, but it must be done on a regular basis to have long-term benefits. Furthermore, fat mass is recovered to a higher extent after intentional weight loss than lean mass in those who do experience weight regain further contributing to the worsening of IR. Finally, some good benefits of modest weight loss in people who eat high-DF diets are likely to contribute to lower IR and the chance of developing T2DM.[7,20]

The impact of DF (type and quantity) on glycemic control in obese, overweight, and type 2 diabetes patients was examined in numerous reviews and meta-analyses. In a longitudinal analysis of 17 prospective cohorts, an inverse relationship between DF (total DF, cereal fiber, fruit fiber, or insoluble fiber >25 g/day) and the incidence of diabetes was discovered.[21]

Influence of Dietary Fiber Intake on Postprandial Glucose Spikes and Carbohydrate-Rich Food's Glycemic Index

The GI of food is directly proportional to the type and amount of DF.[22] Soluble fiber consumption is linked to the idea of the GI because it slows or prevents the absorption of dietary carbohydrates due to the viscous, gel-forming properties of these fibers, lowering postprandial glucose excursions. In rodent trials, high-GI meals significantly increased body fat mass and IR as compared to low-GI diets. Early-onset (after 3 weeks) and significantly decreased fatty acid oxidation appear to precede these alterations, implying a possible causative role.[23]

However, low-GI diets have not consistently been proven to have favorable effects in human observational studies, which is partially explained by the acknowledged issue of controlling confounding factors such as fiber intake and the lack of acceptable reference diets. Diets with a low GI are usually abundant in fiber. In a randomized, parallel, controlled-intervention study in 210 participants with T2DM, it was reported that moderately decreased concentrations of HbA_1C in patients treated with a low-GI diet as compared to the high-cereal-fiber (HCF) diet over 6 months. However, the low-GI diet in their study contained more fiber than the so-called HCF diet (18.7 compared with 15.7 g. Fiber/1000 kcal; $P < 0.001$), and many of the fibers that were emphasized in the "high-cereal-fiber group" were, in fact, high in soluble types of fiber (i.e. pectins) or starchy high-GI foods such as baked potatoes.[7]

Role of Dietary Fiber in the Reduction of Premature Mortality among People with Diabetes

Diets rich in fiber are an important part of diabetes therapy, since they enhance glycemic control, and lower blood lipids, body weight, and inflammation, as well as lowering the risk of premature death. According to a comprehensive review of the function of DF in diabetes management, increasing daily fiber intake by 15 g or 35 g could be an acceptable objective for reducing the risk of premature mortality in persons with diabetes. These advantages were not limited to any fiber type or type of diabetes, and they were shown across the intake spectrum, while those going from low-to-moderate or high intakes saw higher improvements in glycemic control.[24]

Effect of Fermentable Dietary Fiber Consumption on Short-chain Fatty Acid Synthesis and Gut Microbiota Composition

A large number of interventional studies have looked into the effects of fermentable nondigestible carbohydrates on metabolic management, which has been linked to increased short-chain fatty acid (SCFA) production

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in the colon. High levels of SCFAs are thought to be advantageous (by lowering hepatic glucose production and enhancing lipid homeostasis) and may also affect the gut microbiota's makeup.[22] It has been suggested that the relationship between amino acid metabolic profile and IR could be linked to particular gut microbiota members. Significant correlations of serum branching chain amino acids (BCAAs) with IR were found in a recent study that combined measures of IR with metabolomics and microbiome shotgun sequencing in humans. These correlations were linked to increased microbial production and reduced microbial transport mechanisms for BCAAs, explaining the increased BCAAs.[25]

Furthermore, in intervention studies in overweight and obese humans, consuming supplemented, isoenergetic, high-plant-based-protein diets compared to HCF resulted in large and significant differences in IR, but the composition of dominant groups of the gut microbiota was not affected by the diets, and the cereal fiber extract used was neither fermented *in vivo* nor *in vitro*, indicating that other mechanisms were involved that conveyed improved IR on the gut microbiota. Cereal fiber interfering with dietary protein absorption is a unique mechanism that could explain why people who eat high-fiber diets have better IR.[26]

Additional Possible Pathways That May Help to Explain the Improved Metabolic Effects of High-fiber Diets

Several alternative theories have been offered to explain the positive metabolic effects of high-fiber consumption. The effects of fiber consumption on IR, gut hormones, adipokines, inflammatory markers, and the composition of the gut microbiota are all explored in most research publications, but the majority of the clinical studies have focused on aspects of fiber intake that can be related to soluble, viscous, fermentable fibers or metabolically active compounds. Insoluble cereal fibers are the form of DF that has proven preventive benefits against the development of T2DM.[7,27]

Recommended Dietary Fiber Intake

The amount of fiber is recommended based on energy intake. Fiber intake of 30 g/2000 kcal is considered to be safe as per ICMR-National Institute of Nutrition, India, 2020.[28] The United States Department of Agriculture (USDA) Dietary Guidelines for Americans recommend that fiber intake in the general population be around about 25 g/day–28 g/day for women and 31–34 g/day for men. According to the American Diabetes Association, persons with diabetes should consume the same amount of fiber as the general population. Regarding the preferred DF ingestion types, no recommendations have been offered in detail, although it is advised that ≥50% of all grains taken should be whole grains. It has been acknowledged that a fiber intake of >50 g/day is difficult to achieve without the use of DF supplements.[28,29]

Most commonly used DF supplements are primarily soluble-fiber types, such as hydrolyzed guar gum, glucomannan, xanthan gum, psyllium, pectin, alginate, β-glucan, inulin, resistant maltodextrin concentrates, and various fiber combinations.[30]

Conclusion

Despite a plethora of information accumulated over many decades to support the various health advantages of DF, the health dangers of a diet short of fiber, and the related attempts to educate the public, our diets in the modern world remain deficient in fiber.[13]

DF intake has declined through the years due to changes in food habits. An increased intake of sugar, refined foods, and processed fats is altering our gut microbiome. This is triggering inflammatory and oxidative stress microbiome. This emphasizes the necessity to work on the improved integrity of the gut. DF has varied benefits with evidence-based support. Fiber works as a prebiotic along with increased antioxidants, phytochemicals, and flavonoids. Intake of this not only supports good health but always prevents various noncommunicable diseases such as lipids, obesity, and diabetes. In both people with diabetes and people without diabetes, increasing soluble fiber consumption increases insulin sensitivity.[3]

Thus, when making food selections, it is crucial to pay attention to fiber content labeling. This food composition information is vital for consumer food choice behavior and may influence the food selection that is beneficial for better health outcomes. Fortification of foods extracted or synthesized with nondigestible carbohydrates or employing them in dietary supplements also constitutes a strategy to increase fiber intake.[31]

Limitations

This is a narrative review. We need more systematic reviews and interventional studies that focus on the importance of DF in diabetes management.

Financial support and sponsorship

Nil.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Examination of Feet in People with Diabetes: A Guide for Primary Care Physicians

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Abstract

Diabetic foot is a common complication of diabetes and leads to considerable morbidity and mortality. Neuropathy, deformity, infection and ischemia play a key role in the pathogenesis of diabetic foot ulcer. A multidisciplinary team approach by a nurse, physician, diabetic foot surgeon and the caregiver as well as close monitoring can prevent foot complications. Proper foot care, foot hygiene, annual foot examination and correct choice of footwear are main factors in preventing foot problems, ulceration and amputations. Physicians play a lead role in early detection and prevention of foot problems. This article will focus on how to perform foot examination in routine clinical practice.

Keywords: Diabetes mellitus, diabetic foot, neuropathy

Introduction

Among the long-term complications of diabetes, diabetic foot (DF) problems are considered among the most common and costly complication of diabetes.[1] Three major reasons for DF include long duration of diabetes or uncontrolled diabetes, peripheral neuropathy, and peripheral arterial disease (PAD).[2] Nearly 50% of patients with diabetes are affected by peripheral neuropathy in their lifetime.[3] The global prevalence of peripheral neuropathy is estimated to be between 6% and 51% among adults with diabetes, depending on age, duration of diabetes, glucose control, and the type of diabetes.[4] In India, the reported prevalence of diabetic peripheral neuropathy (DPN) ranges from 8% to 59%.[5] Every year approximately 40,000 legs are being amputated, of which 75% are due to neuropathy and infection.[6] Peripheral neuropathy is the damage of nerves that affects the legs and feet, rarely arms and hands, in people with diabetes. This results in loss of protective sensation (LOPS) and symptoms such as numbness, tingling, burning, electric shock like sensation, paraesthesia, allodynia, and hyperesthesia in feet and legs.[4] Neuropathy is not only painful and distressing but may also lead to major complications such as ulcers, disability and lower limb amputation. Around 15% of patients with diabetes are at risk of developing foot ulcers in their lifetime, 14%-24% of which require amputation.[7]

The condition is often diagnosed late when irreversible damage has already taken place. The reason is that people with diabetes may not have any primary foot-related complaints. The development of DPN is insidious, subtle, and the individual might be asymptomatic.[8] Rather, foot problems are silent and most of the time, it is the relatives who notice a wound or an ulcer in the patient's foot, or it is detected during a routine checkup.

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Quick Response Code:

Website: www.cdrpj.org

DOI: 10.4103/cdrp.cdrp_11_22

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Submitted: 23-May-2022 **Revised:** 17-Oct-2022
Accepted: 26-Oct-2022 **Published:** 07-Jul-2023

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How to cite this article: Tathare SR, Kumbhar VN, Panse RJ, Kumaran S, Deshmukh S, Bidaye A. Examination of feet in people with diabetes: A guide for primary care physicians. Chron Diabetes Res Pract 2023;2:90-7.

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According to studies in rural South India, age, sex, increased body mass index, and advancing duration of diabetes control are the factors that contribute to the development of DPN.[9]

In developing countries, some other factors are still prevailing, such as barefoot walking, illiteracy, low socio-economic conditions, and ignorance about DF care by the primary care physicians that contribute to high prevalence of diabetic foot problems.[6]

Above all, the economic burden due to the loss of productivity or absenteeism from work, cost of treatment, hospitalization, morbidity, and mortality is considerable.[10]

It has been reported that good diabetes control and proper foot care resulted in a 50% decrease in foot amputations.[11] Education of patient, nurse, physician, and caregiver, along with close monitoring, reduced the foot complications by 49%-85%.[12] Foot care, proper foot hygiene, annual foot examination, and a correct choice of footwear are the key to a healthy foot.[13]

Physicians play a lead role in the early detection and prevention of foot problems. People with diabetes should follow-up with their physician regularly. Taking history and doing the general and systemic examination, including of the feet, are an integral part of the visit. Foot examination is an important aspect of diabetes management, which should never be missed.

The objective of the article is to focus on a detailed foot examination, intense proactive screening, identification of risk, and early intervention for DF problems, thus preventing major complications, particularly at the primary physician level.

Pathogenesis of Diabetic Foot

Neuropathy, infection, and ischemia are the classical triad that contributes to the pathogenesis of DF [Figure 1].[14] Long-standing or uncontrolled diabetes leads to small and large fiber neuropathy, also called distal symmetrical peripheral neuropathy; the extent of which may be mild, moderate, or severe.[15] This results in LOPS in the feet. An insensate foot is more prone to repeated trauma which often goes unnoticed and results in typically painless wounds. Motor neuropathy leads to limited joint mobility, and structural deformities, leading to abnormal plantar pressure and skin breakdown [Figure 2].[16] PAD, if any, results in reduced blood flow and thus delay in wound healing [Figure 1].

If the foot ulcer is not appropriately attended, it may lead to major surgery or amputation [Figure 2].

Charcot foot or Charcot neuroarthropathy (CN) is another serious and limb-threatening complication of uncontrolled diabetes. It affects bones, joints, and soft tissues in the foot and ankle, involving osteolysis (bone destruction), subluxation, dislocation, and deformity.[17] These changes result in collapsed joints and severe pedal

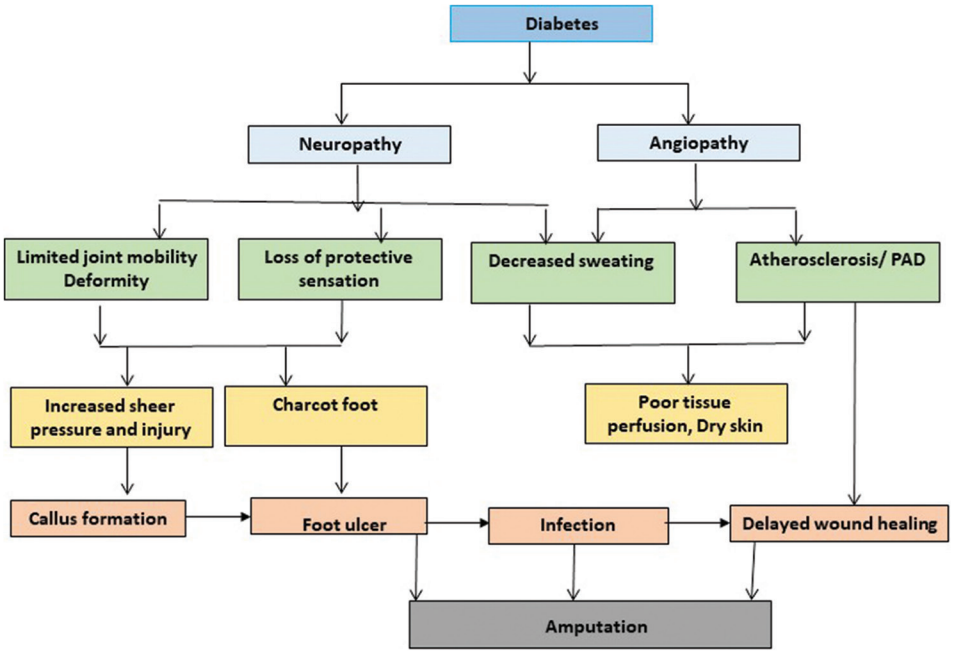


Figure 1: Pathogenesis of diabetic foot ulcer

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Figure 2: Complications of peripheral neuropathy. Image courtesy: Chellaram Hospital, Diabetes Care and Multispeciality

deformities. The most common joint to collapse in CN is the tarsometatarsal joint, which leads to a rocker bottom deformity [Figure 2].

Examination of Feet

The following aspects need to be considered during the examination of feet which involves history taking, clinical examination, footwear examination, diagnostic tests and risk evaluation [Figure 3].

History

A detailed history and thorough foot examination, after removing shoes and socks, should be done in a well-lit room at each visit.

The duration and control of diabetes should be enquired. Long-standing diabetes with uncontrolled high blood glucose levels can damage the nerves, especially in the legs and feet.[18]

History of accident, injury, fracture, sprain, infection, surgery, previous ulcerations, amputation, or nail avulsion (traumatic or surgical) and barefoot walking practice needs to be enquired.

Enquire about painful symptoms such as burning, tingling, pricking, electric shock-like sensation and silent symptoms such as numbness, cotton wool-like sensation on the soles, slipping of footwear while walking and imbalance.

Symptoms of PAD, such as cramping, pain in calves, thighs, and buttocks that increase with walking and are better after rest (claudication), should be enquired for.[19]

Smoking or tobacco consumption in any form should be enquired as its is a direct risk factor for PAD.[20] It can exacerbate diabetic peripheral sensory, autonomic, and motor neuropathy and thus contributing to foot ulceration, and also hinders wound healing.[21]

History regarding alcohol intake is important. There is a greater prevalence of PN in people with diabetes with chronic alcohol consumption.[22]

Clinical Examination

Despite having nerve damage, some people may not have any of the above symptoms; hence, the next important aspect of management involves examination and finding the signs of neuropathy or any abnormalities/deformities.

Dermatological Examination

The color of the skin of the feet and legs should be checked. Any change in color like erythema, blackish discoloration, pigmentation of skin, or presence of ulcer should be noted. Redness, swelling, and warmth in the leg or foot indicate cellulitis. In wet gangrene, the part of the foot looks pale, bronze to purple red, while it appears dry, dark and mummified in dry gangrene.[23]

Dryness of feet and legs, which is a sign of neuropathy and poor circulation and scaly skin, should be noted.[14] Maintaining adequate hydration of the skin is extremely important to prevent dryness and fissures [Figure 4], which can serve as a portal of entry for infection. Bacterial and tenia pedis infections are the common reasons for infections and ulcerations in people with diabetes.[6,24]

The local temperature should be checked with the dorsum of the hands. Any significant difference as compared to the contralateral foot should be evaluated further for any underlying cellulitis or infection.[25] A temperature of greater that 3-4° celsius compared to the contralateral foot may be an indication of infection or acute Charcot foot.[26]

Any hard skin areas or high-pressure points or calluses should also be checked.

The callus is hyperkeratosis of the skin caused by excessive mechanical, shear stress, foot deformity, limited joint mobility, repetitive stress while walking or due to ill-fitting shoes.[27] Callus on the plantar aspect or malleolus or on

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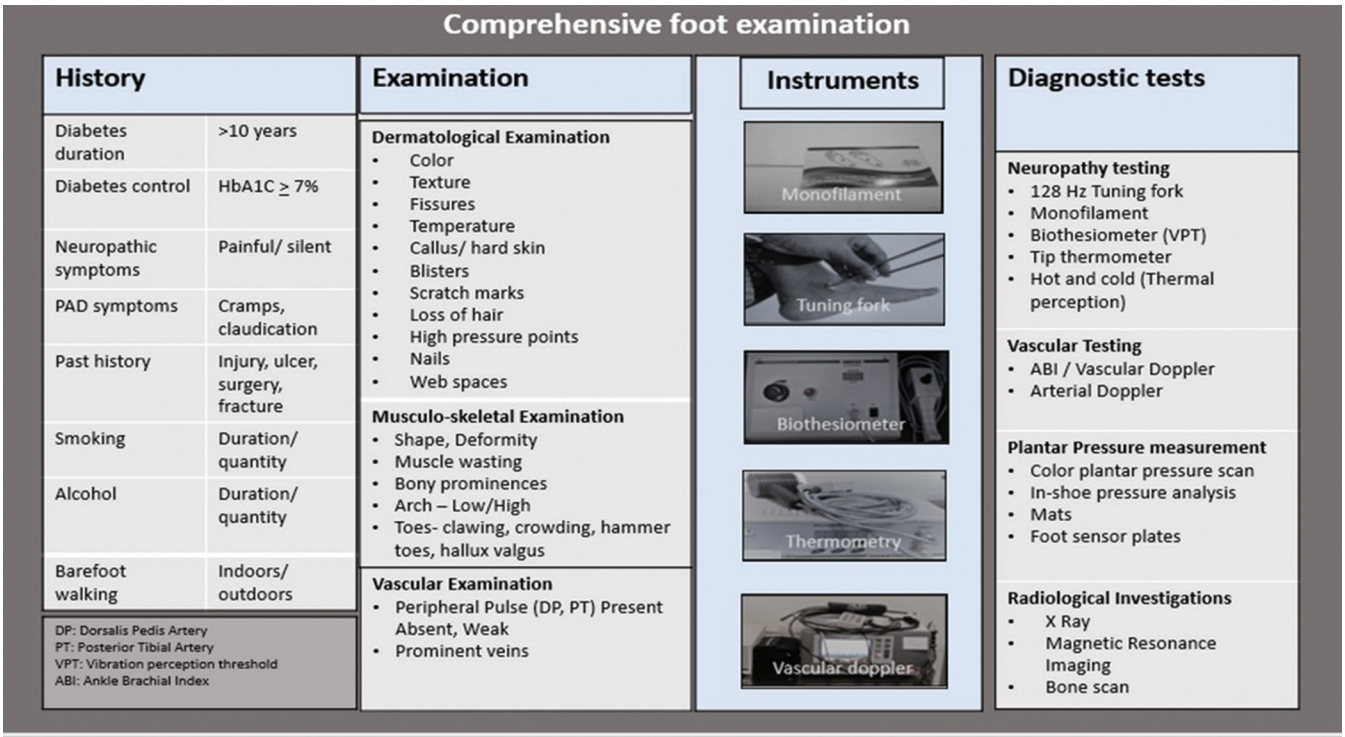


Figure 3: A quick guide for foot examination

bony prominences may lead to infection, hemorrhage, or ulcers if not given adequate care [Figure 4].

Any corn in feet should be looked for. Corns may be multiple or single, recurrent, deep or superficial, painless or painful. Painful and infected corn needs intervention. Any old healed injury marks, surgical scars should be looked for.

The presence of any blisters should be checked for. Exposure to heat and ill-fitting footwear may lead to blisters, which can go unnoticed if a person has peripheral neuropathy and may lead to complications such as infection and ulcers.

Nails: Brittle toe nails, ingrowing nails, nails growing with the skin or fungal nail infections are commonly found in individuals with diabetes [Figure 4]. Nail trimming technique should be checked; if wrong, the correct way to trim the nails should be explained.

Loss of hair on the legs may be an indication of peripheral neuropathy and poor perfusion.[7] Guttering between the metatarsals due to muscle wasting should be checked.

Any scratch marks should be checked for. Many people have a complaint of itching due to dry skin (autonomic neuropathy). Scratching opens up the skin, which may allow infection to set in. Any bad odor from the feet should be taken note of. Poor foot hygiene and web space fungal infections give bad odor to the feet.

Web spaces: Interdigital fungal infections are common in individuals with diabetes [Figure 4]. This occurs due to clawing and crowding of toes and the inability to maintain good foot hygiene because of obesity, impaired vision, or advanced age.[28]

Musculo-Skeletal Examination

Shape/deformity

Motor neuropathy leads to deformities, changes in the shape of the foot, and leads to abnormal bony prominences [Figure 2] and pressure points, which gradually cause skin breakdown and ulceration. Any change in shape, loss of arch, flat foot, low arch, high arch, bony prominences need to be checked. Look for clawing [Figure 4] of toes which is caused due to metatarso phalangeal joint hyperextension and proximal interphalangeal joint (PIPJ) flexion, hammer toes which are caused due to distal interphalangeal joint (DIPJ) extension[16], hallux valgus, bunion, crowding or overlapping of toes. Advanced foot deformity like Charcot foot should to be looked for [Figure 2].

Vascular Examination

Peripheral pulses

Patient experiences claudication-like pain (pain in the legs while walking which is relieved with rest) if blood

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Figure 4: Few illustrations of findings in neuropathic foot. Image courtesy: Chellaram Hospital, Diabetes Care and Multispeciality

flow is hampered. Blood flow in feet is important for wound healing, wounds may lead to gangrene if blood flow is inadequate.

Two main arteries to be palpated are the dorsalis pedis artery (DPA) and the posterior tibial artery (PTA). Pulse may be weak, normal, bounding, absent or may not be felt due to swelling. Weak or absent pulse and cold feet indicate peripheral vascular disease.[20] Any abnormality should be evaluated further. Advanced tests like Ankle Brachial Index (ABI) and Arterial Doppler are recommended.

Footwear Examination

Poor-fitting footwear can lead to frictional injury, blisters, calluses and ulcers, leading to major issues. Properly fitting footwear can reduce foot problems and amputation by up to 85%.[28] Footwear should not be too tight or too loose; toe box should be wide enough to allow the free movements of the toes. It should have a strong heel counter to give sufficient stability, smooth inner linings, tough but lightweight outsole to absorb the sheer forces and Velcro to adjust the shape of the foot and deformity, if any. Footwear should be bought in the evening time when the foot size is generally more due to swelling (IWGDF guideline 2019-The International Working Group on the DF).[36]

Diagnostic Tests

Assessment for neuropathy

After a detailed examination, bedside testing for neuropathy with simple instruments can be performed, which includes a 128 Hz tuning fork and Semmes-Weinstein Monofilament.

The 128 Hz tuning fork can be used to check vibratory perception. A tuning fork should be set in vibration and kept on metatarsophalangeal joint of the big toe. The person is asked to respond to whether he or she can feel the vibration and also when it stops. Immediately, it is placed on the wrist of the person. If the vibration is still felt on the wrist, it indicates that the person has impaired vibratory perception.[29]

Ten gram Semmes-Weinstein Monofilament is a simple, noninvasive tool used to check protective sensation in the feet. A 10 g monofilament is kept perpendicular to the skin on the big toe, metatarsal heads, instep, and heels, and pressure is applied till it buckles to form C shape, which exerts 10 g weight.[12] Nine sites on the plantar and one on the dorsum are tested. The ability to feel on seven or more sites is indicated as normal, <7 sites is indicative of LOPS.[30]

Advanced tests such as Biothesiometry and thermal perception test (hot and cold) are recommended to evaluate the nerve function [Figure 3].

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Biothesiometer, also known as Vibrometer, is an electromechanical instrument used to identify large fiber neuropathy even at the subclinical stage. Gradually, increasing vibration is delivered at various points on soles, and the threshold at which vibration is perceived is noted [Table 1].[31]

For small fiber neuropathy, temperature sense is tested with an instrument called Tip thermometer or test tubes with hot water (35-45 degrees Celsius) or cold water (5-10 degrees Celsius) directly placed on the skin, and the loss of temperature sense is graded as normal, weak or loss.[31]

Advanced diagnostic tests such as sensitometers or thermometry and nerve conduction studies are also available in tertiary centers.

Different scoring systems are followed, such as the Michigan neuropathy screening instrument (MNSI), Toronto clinical scoring system, neuropathy symptom score, and neuropathy disability score.

MNSI includes a set of 15 self-administered questionnaires along with vibration perception and ABI values. A score of 7 or less is conclusive of neuropathy.[32]

Assessment of Circulation

ABI is a very useful test to assess arterial blood supply. The patient should be in a supine position at least 20 min before the test. Systolic pressures of the brachial artery, PTA and DPA are measured using an 8 mm Hz probe of Handheld Doppler, and ABI is calculated[30] [Table 2].[31]

Assessment of Plantar Pressure

Abnormally high plantar pressure in an insensate foot is a major contributing factor in the development of DFU. Hence, the assessment of plantar pressure and strategies for reduction and equal distribution of the same is important.

Different devices such as mats, color plantar pressure scans, foot pressure sensor plate, in shoe pressure analysis are available.[33]

Radiological Assessment

X-ray, magnetic resonance imaging, or the three-phase technetium-99 m methylene diphosphonate bone scan may be helpful in diagnosing acute bone pathology to rule out fracture and Charcot neuropathy.[25]

Risk Evaluation

The foot may be normal, with intact nerve function, normal blood flow, and no deformity (risk zero); otherwise can be categorized as Risk 1, 2, or 3 depending on the neuropathy status, blood flow, and the presence of or history of foot ulcers.[1] Based on risk assessment, further management of the patient is suggested. It may just be regular follow-up, the duration of which is determined by the risk, such as yearly, six monthly or quarterly, footwear modification, or even surgical procedures to prevent further complications [Table 3].

International Diabetes Federation (IDF) 2018 has designed a pocket chart in the format of Z card with information for health professionals to identify, assess, and treat DF patients earlier in the "window of presentation" between when neuropathy is diagnosed and before developing an ulcer.[34]

Pocket chart from the American Diabetes Association is also available as a guide for physicians for comprehensive foot examination.[35]

There are different classification systems of DFU, namely the University of Texas Wound Classification System,

Table 1: Interpretation of vibration perception threshold and risk

	VPT	
VPT in volts	Grade	Risk
<15	0	Normal
16-24	1	Intermediate
>24	2	High risk

VPT=Vibration perception threshold

Table 2: Interpretation of Ankle Brachial index and peripheral arterial disease risk

ABI value	Interpretation
0.9-1.4	Normal
0.8<0.9	Mild
0.5<0.8	Moderate
<0.5	Severe
>1.4	Calcification of arteries

ABI=Ankle Brachial index

Table 3: Follow-up recommendation based on risk evaluation

Risk Category	Clinical status	Recommendation
Risk 0	Normal plantar sensation	Yearly foot check up
Risk 1	LOPS	Half yearly check up
Risk 2	LOPS High pressures Deformity	Quarterly foot check up
Risk 3	Previous Ulcer Amputation Neuropathic fracture	Customized footwear Surgical intervention

LOPS=Loss of protective sensation

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Table 4: Texas classification of diabetic foot ulcer

Stage	Grade			
	0	1	2	3
A	Preulcerative lesions, no skin break	Superficial wound, no penetration	Wound penetrating tendon or capsule	Wound penetrating bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

Table 5: Foot care education

Foot care education	
Do's	**Don'ts**
Daily inspection	Barefoot walking
Skincare	High heels and footwear with toe grip
Web space care	Self-treatment/self-surgery
Correct nail-trimming technique	Massaging the legs and feet
Use of appropriate footwear	Hot fomentation/cold compresses
Use footwear with socks	Corn caps
Shop for shoes at the end of the day when the foot size is bigger	Smoking/alcohol
Apply moisturizer, avoid between the toes	Walking in the presence of foot ulcer

Source: Michael Dansinger; Diabetes Foot Care; Web med/on May 18, 2021, https://www.webmd.com/diabetes/caring-feet

Wagner's Classification of DF, PEDIS, King's classification, Kobe's Classification, Amit Jain's Classification, Van Acker Classification, S(AD)SAD system/ Classification, Sindbad, International working group on DF, etc.[36] Texas and Wagner's classification are commonly used in a primary care setting of which the Texas classification system has been summarized in Table 4.

Foot Care Education

Foot care education plays an important role in preventing foot problems. Instructions should be given to patients and their caregivers regarding daily examination, proper foot hygiene, nail care, appropriate footwear along with socks, both indoors and outdoors and maintaining proper moisture of feet by using emollient. The importance of avoiding barefoot walking, any thermal exposure, chemical agents, and avoiding self-treatments or self-surgeries should be clearly explained [Table 5].[36]

Conclusion

Individuals with diabetes should regularly visit a foot care specialist. At least a yearly foot examination is recommended, which helps to diagnose the problems at the early stage, which can be treated accordingly. Management of DF includes primary prevention by regular screening, foot care education, and appropriate footwear advice; secondary management by treating trivial foot lesions such as callus, blister, or nail pathologies, and tertiary measures by aggressive treatment of advanced foot lesions such as infection, ulcers, or gangrene, thus achieving significant limb salvage and prevention of amputation.[6]

Regular and comprehensive foot check-up, appropriate foot care knowledge, proper footwear and adequate glycemic control are the keys to preventing foot problems in patients with diabetes mellitus. Physicians, patients, and caregivers play an important role in maintaining healthy feet.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Insulin Autoimmune Syndrome: A Report of Two Cases

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Abstract

Insulin autoimmune syndrome (IAS), also known as Hirata's disease, is a rare endocrine disease. It is a form of autoimmune endogenous hyperinsulinemic hypoglycemia, which develops when genetically predisposed individuals get exposed to triggering factors such as viral infection or certain medications containing sulfhydryl groups. It is important to consider IAS in the differential diagnosis of hypoglycemia as its incidence seems to be increasing worldwide. In this article, we summarize a report of two cases of IAS and their clinical manifestations, biochemical characteristics, their step-by-step diagnosis, and also prompt utilization of continuous glucose monitoring system as a monitoring tool for appropriate management. The first patient who presented with hypoglycemic episodes had recently suffered from a viral pneumonia, which probably acted as a superantigen and triggered development of IAS. The second patient also had hypoglycemic episodes, which used to recover after intake of glucose-containing liquids. Alpha-lipoic acid containing multivitamin may have triggered the development of IAS in the second patient. The tests performed showed high serum insulin and C-peptide levels along with insulin autoantibody positivity confirming the diagnosis of Hirata's disease. Immunosuppression therapy was not required as both the patients responded well to diet modification and corticosteroid therapy. It is important to be mindful while prescribing alpha-lipoic acid-containing supplements though it has good antioxidant properties, as it is presumed to be associated with increasing number of IAS cases.

Keywords: Alpha-lipoic acid, hypoglycemia, insulin autoantibody, insulin autoimmune syndrome

Introduction

Diagnosis of autoimmune forms of hypoglycemia can be challenging and requires close monitoring and appropriate evaluation as they are relatively rare in routine clinical practice. Autoimmune forms of hypoglycemia are of two types: insulin autoimmune syndrome (IAS) in which antibodies are directed against endogenous insulin and the other being Type B insulin resistance syndrome which is characterized by the presence of anti-insulin receptor antibodies.[1,2] IAS is characterized by recurrent spontaneous episodes of fasting or postprandial hypoglycemia in individuals who are not previously exposed to exogenous insulin and who did not carry any pathological abnormalities of pancreatic islets.[2,3]

The key factors in the diagnosis of IAS, also known as Hirata's disease, are high levels of serum insulin, the presence of high serum concentration of insulin autoantibodies (IAAs), and Whipple triad, i.e., symptoms or signs of hypoglycemia along with documented low plasma glucose concentration and resolution of hypoglycemia symptoms or signs after glucose administration.[4] Patients of IAS present in adulthood, usually over 40 years of age, and it seems to affect both the genders equally.[3-5] From its first description till the year 2009, at least 380 cases of IAS have been identified in Japan. IAS is a leading cause of hypoglycemia in

Access this article online

Quick Response Code:

Website: www.cdrpj.org

DOI: 10.4103/cdrp.cdrp_24_22

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Submitted: 10-Dec-2022 **Revised:** 05-Jan-2023
Accepted: 16-Jan-2023 **Published:** 20-Feb-2023

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How to cite this article: Deshmukh S, Purandare VB, Pakale A, Unnikrishnan AG. Insulin autoimmune syndrome: A report of two cases. Chron Diabetes Res Pract 2023;2:98-103.

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Japan but is rare in non-Asian population; however, the incidence is increasing worldwide.[6,7] We summarize our experience of two cases of this rare disease. Informed consent was obtained from the patients for the publication.

Case Reports

Case 1

A 66-year-old woman was referred to us by a physician for the further evaluation of hypoglycemic episodes. Her medical records revealed that she was recently admitted at the nearby hospital for viral pneumonia and was managed with intravenous amoxicillin and potassium clavulanate, oral oseltamivir, antihistaminic with acebrophylline, and diethylcarbamazine. She received nebulization with bronchodilators, and intravenous hydrocortisone had also been given. During hospitalization, her glycated hemoglobin (HbA_1C) was 6.6%. She was discharged on oral antihistaminic, bronchodilator rotacaps, metformin, and low-dose oral prednisolone by the treating physician.

After discharge, she developed hypoglycemic episodes early morning for 3–4 days and experienced symptoms such as sweating, fatigue, increased hunger, and palpitations. Following this, on advice of the treating physician, the patient stopped taking metformin and prednisolone. After stopping metformin, she continued to experience hypoglycemic episodes with capillary blood glucose of 54 mg/dl documented on glucometer during the episode. The symptoms used to get better after taking fruit juice or carbohydrate-rich meal. She was brought to our outpatient department (OPD) clinic and was hospitalized for further evaluation.

Physical examination showed body mass index of 28.77 kg/m^2 and her vital parameters were stable. There was no thyroid gland enlargement or acanthosis nigricans. No signs of systemic lupus erythematosus or thyrotoxicosis were present. Systemic examination was within normal limits. Past medical history was suggestive of long-standing hypertension and childhood asthma, which were well controlled with medications.

Routine laboratory investigations were within normal limits including hemogram, thyroid profile, renal and liver function tests, urine routine, and microscopy. During hypoglycemic episode, her random C-peptide was 18.8 ng/mL and her fasting C-peptide was 23.42 ng/mL (normal range: 1.1–4.5 ng/mL). Her serum insulin was >300 μU/mL (normal range: 2.6–24.9, peak up to 166 μU/mL). We performed Synacthen test and the basal cortisol level were measured at 30 min and 60 min after giving intramuscular injection of Synacthen 250 mg. The basal serum cortisol level was 8.9 μg/dl (normal range: 5–25 μg/dl), the 30-min poststimulation cortisol level was 21.1 μg/dl, and the 60-min poststimulation cortisol level was 24.5 μg/dl, which suggested a normal response. High serum insulin and raised C-peptide levels were suggestive of hyperinsulinemic hypoglycemia, either insulin antibody syndrome or insulinoma. Ultrasound and contrast-enhanced magnetic resonance imaging (MRI) of the abdomen were done which did not show any abnormality or lesion in the pancreas. Meanwhile, the report of serum insulin autoantibody done using ELISA kit (Aeskulisa, Wendelsheim, Germany) was positive at 61.5 U/mL (positive >18 U/mL), and hence, the diagnosis of IAS was confirmed.

During hospitalization, we had put the patient on freestyle libre (Abbott) continuous glucose monitoring (CGM). Initially, the CGM showed hyperglycemia followed by fasting low blood glucose levels [Figure 1a]. The hypoglycemia episodes largely improved once we started the patient on oral prednisolone 1 mg/kg with diet modification, which included small frequent low carbohydrate meals and a mandatory bedtime snack. The patient was discharged after 1 week of hospitalization. After 10 days on follow-up in the OPD, the CGM showed resolution of hypoglycemia episodes [Figure 1b]. We gradually tapered and stopped the oral prednisolone over

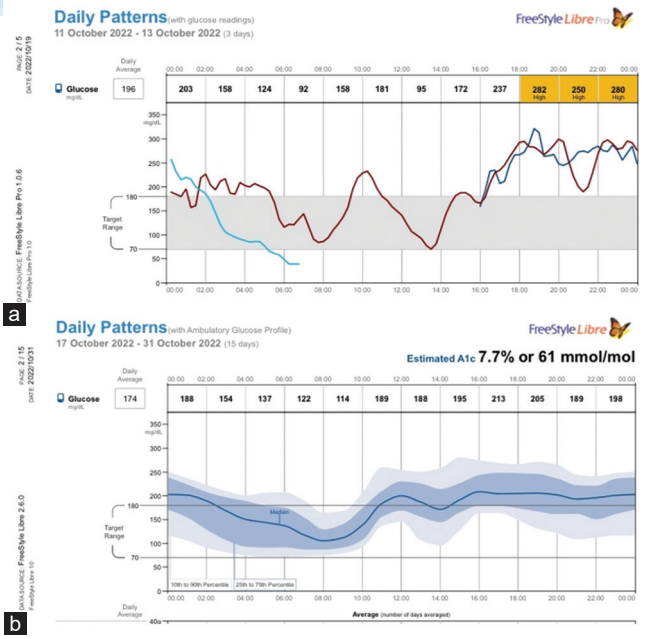


Figure 1: (a) CGM graph representing fasting hypoglycemia. (b) CGM graph representing improvement in hypoglycemic episodes postdiet modification and steroid therapy. CGM: Continuous glucose monitoring