Endotext

DIABETES IN THE TROPICS

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Received December 18, 2024

ABSTRACT

Diabetes mellitus (DM), an important non-communicable disease, is a major global health problem. Of the major three types of DM, namely type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus, T2DM constitutes more than 90% of cases. The diabetes prevalence is on the rise in tropical regions. T1DM, caused by an autoimmune process, is influenced not only by genetic susceptibility but also to a greater extent by environmental factors. Among the multitude of environmental factors viral triggers, environmental toxins, exposure to exogenous antigens, and geographical factors play a significant role in T1DM pathogenesis. The hygiene hypothesis as explained by prevalent helminthic infection in the tropics, intense ultraviolet exposure translating to improved vitamin D synthesis serving as immune modulator, delayed exposure to cow's milk and gluten thereby avoiding the allergen provoking beta cell autoimmunity, are a few of the postulated protective mechanisms for T1DM in tropical regions. Tropical regions comprise almost 40 percent of the world's diabetic load with six countries in the top ten countries with DM. Reports from the IDF also predict a great increase in the coming decades with the maximum increment expected in Africa, Middle East, South-East Asia and South America. The incidence rate of diabetes among those with prediabetes in the Indian subcontinent is also one of the highest reported when compared to the Caucasian population yet comparable to Native Americans and Micronesian populations. World estimates indicate that 16.7% of pregnancies are complicated by some form of hyperglycemia. More than 80% of this is due to gestational DM. While the majority of hyperglycemia in pregnancy is seen in low- and middle-income countries, the prevalence between countries in tropical regions varies with South-East Asian countries topping the prevalence list while Middle East countries and northern Africa show the lowest prevalence (IDF). Diet patterns including greater consumption of tropical fruits with moderate or high glycemic index have been postulated to increase the likelihood of gestational DM. Fibro calculus pancreatic diabetes (FCPD) is a rare but unique and unexplored type of DM found specifically in tropical countries including India, Indonesia, Bangladesh, Sri-Lanka, Brazil and a few African countries. Most of the chronic pancreatitis originates from chronic alcoholism in developed countries contrasting with FCPD, which develops in the absence of alcohol use. Despite rising awareness about DM, the problem of ignorance about DM still exists. Data indicates the alarming fact that one in two adults with DM were unaware of their condition. The increasing incidence and prevalence of

DM in the tropics add to the infectious disease load and severity in the tropics. Infections are an important cause of morbidity and mortality in DM. Although disease duration and glycemic control are important risk factors, ethnicity may also play a role as a risk factor for complications.

INTRODUCTION

Diabetes mellitus (DM), an important non-communicable disease, is a major global health problem. Of the major three types of DM, namely type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational DM, T2DM constitutes more than 90% of cases. According to the International Diabetes Federation (IDF), the prevalence of DM was 537 million with an almost equal number of the population having impaired glucose tolerance, which if not acted upon will contribute to the future burden of DM. Keeping in mind the current trends, the estimated worldwide prevalence of DM in two decades will be 784 million. Despite originally conceived as a disease of the affluent in developed, temperate countries, DM has skyrocketed to an alarming rate in developing tropical countries.

The IDF report also highlights the same fact that the burden of DM is increasing at a more rapid pace in low- as well as middle-income countries in comparison to high-income countries. Apart from geographical differences between tropical and temperate countries, they also diverge in terms of DM in substantial ways. Tropical region includes all the South-East Asian countries, part of Middle Eastern countries, a major part of Africa, South America, and a portion of Australia. Among the top ten countries contributing to the world's DM' burden, tropical countries occupy six slots including India which solely harbors one sixth of the world's burden. Not only the disease burden, but also the pattern, types, demography, and epidemiology of DM is considerably different in tropical regions in comparison to the rest of the globe. It is also highlighted that most countries in tropical regions show lower rates of DM disease detection and limited access to management measures.

History dates to almost a century ago when the distinct aspects of people with DM in the tropics were beginning to be acknowledged as evidenced by an opinion by Sir Havelock Charles in the British Medical Journal (1). In 1950s Hugh Jones reported an unclassifiable form of DM in a small proportion of people with DM in Jamaica which he named as J-type (Jamaican type) (2). J-type was different from the then recognized two major forms of DM namely insulin dependent and noninsulin dependent DM in having mixed characteristics like young onset of disease, ketosis resistance, lean body habitus but with insulin resistance. Similar forms of DM were reported from the Indian subcontinent and Africa (3,4). With observation and follow-up, the clinical spectrum became more inconstant and perplexing with some patients becoming insulin independent, while a few becoming ketosis prone (5).

Amplifying the perplexity, abundance of nomenclature like tropical diabetes, Z-type, M-type, type 3 DM, pancreatic DM, malnutrition- related DM, fibro-calculous pancreatic DM, protein-deficient pancreatic DM, etc. exist. The WHO study group in 1985 recognized this group of DM and conglomerated it as a distinct entity naming it as malnutrition–related DM and also put forward the existence of two subtypes: protein-deficient pancreatic DM and fibro-calculous pancreatic diabetes (FCPD) (8). Likewise, a consensus statement from a workshop conducted in India also drew attention to those special types of DM peculiar to the tropics (6). Yet the most recent WHO classification of DM categorizes FCPD in the other specific types of DM (WHO 2019). Strangely, T2DM, which is the most common form of DM even in tropical regions has been overlooked when DM in the tropics is discussed. This review discusses the various aspects of all forms of DM in the tropics.

EPIDEMIOLOGY

The prevalence of DM is on the rise globally, including in tropical regions. The epidemiology of all types of DM in the tropical region is as follows.

Type 1 Diabetes Mellitus

The global prevalence of T1DM in children and adolescents below 20 years is estimated to be more than one million (IDF). T1DM, caused by an autoimmune process, is influenced not only by genetic susceptibility but also to a greater extent by environmental factors. Among the multitude of environmental factors viral triggers, environmental toxins, exposure to exogenous antigens, and geographical factors play a very significant role in T1DM pathogenesis (7,8). The prevalence of disease follows a latitudinal gradient showing a direct relationship with the distance from the equator. Tropical regions show a lower prevalence while European countries exhibit a higher rate (9).

The incidence rates are highest in the northern European population and not surprisingly among the top ten countries based on incidence rates of T1DM, only one tropical country is included (IDF). The hygiene hypothesis as explained by prevalent helminthic infection in the tropics, intense ultraviolet exposure translating to improved vitamin D synthesis serving as an immune modulator, delayed exposure to cow's milk and gluten thereby avoiding the allergen provoking beta cell autoimmunity are a few of the postulated protective mechanisms for T1DM in tropical regions (10–12). Data from temperate regions suggest the onset of T1DM occurs more often in winter while such differences were not shown in tropical countries (13,14). Likewise, the prevalence of anti-islet cell antibodies seems heterogenous in studies with some showing concordance to Western data while others showing higher antibody negative T1DM in tropical countries than in Western countries, although the number of antibodies tested vary between studies (15–17).

Type 2 Diabetes Mellitus

DM is estimated to affect around one-tenth of the adults aged 20-79 years of which the major type is T2DM. Tropical regions comprise almost 40 percent of the world's diabetic load with six countries in the top ten countries with DM. Reports from the IDF also predict a rampant increase in the coming decades with maximum increment expected in the tropical regions (Africa, Middle East, South-East Asia, and South America). This increase in DM could be due to increasing life expectancy, improved access to health care, urbanization, and Westernization of lifestyle (18). Poorer lifestyle in the form of unhealthy food options, inaccessible recreational physical activity, and lack of awareness of healthy living accelerate the DM risk. Much evidence for T2DM in the tropics come from India which throws light on the distinguishing features from that of the Western population. The distribution of DM in developed nations is predominantly among the underprivileged strata whereas in developing countries including India, DM has been a disease of the affluent populations. However, it is bothersome to note that the prevalence is now increasing even among the lower socioeconomic strata. The nationwide study which investigated the epidemiology of DM in India showed that the prevalence was higher in urban in comparison to rural areas, although the rate of prediabetes is comparable in urban and rural areas thereby projecting that rural areas will reach the DM numbers akin to urban regions in the near future (ICMR) (19). Higher socioeconomic status remained a risk factor for DM in rural areas while the same was not true in urban areas reflecting the epidemiological transition in urban areas, probably owing to improved health awareness among higher socioeconomic strata. It was also shown that male sex is considered an independent risk factor for developing DM, which is at variance to what is shown in temperate zone showing female preponderance. The plausible explanation for this disparity between regions could be due to neglected healthcare among women in certain communities. Likewise, evidence from the same study

did not favor smoking and alcohol as independent risk factors for DM, which contrast with the data from wealthier nations.

The incidence rate of DM among those with prediabetes in the Indian subcontinent is also one of the highest reported when compared to the Caucasian population yet comparable to the Pima Indians, Native Americans, and Micronesian population (20). Besides it is also interesting to note that Asian Indians develop DM at younger ages and at lesser obesity levels as compared to Western counterparts. This could be explained by virtue of South Asians having higher abdominal fat, more insulin resistance, and higher C-reactive protein levels despite lower body mass index (21,22). Among the individuals with prediabetes, prevalence of impaired fasting glucose is higher than that of impaired glucose tolerance in Asian Indians. This finding is in accordance with the evidence that an insulin secretory defect plays a significant role in T2DM pathogenesis in Indians compared to other ethnicities (1). This is also in line with the evidence from IDF which shows that age adjusted prevalence of impaired glucose tolerance is lowest in the southeast Asian region while that of impaired fasting glucose is considerably higher in southeast Asian region than other regions.

Hyperglycemia in Pregnancy

World estimates indicate that 16.7% of pregnancies are complicated by some form of hyperglycemia. More than 80% of this is due to gestational DM. While the majority of hyperglycemia in pregnancy is seen in low- and middle-income countries, the prevalence between tropical countries is vast with South-East Asian countries topping the prevalence list while Middle East countries and northern Africa show the least prevalence (IDF). Studies have also elucidated the possible effect of season and temperature on the prevalence of gestational DM with increased prevalence in summer and higher temperature (23,24). Factors like diet patterns including greater consumption of tropical fruits with moderate or high glycemic index have been postulated to increase the likelihood of gestational DM (25).

Maturity Onset Diabetes of the Young

The pioneering reports from Fajans and Tattersal described an intermediate form of DM different from the two classical forms of insulin dependent and non-insulin dependent DM (26). They coined the term Maturity Onset Diabetes of the young (MODY) showcasing its characteristics of age of onset below 25 years, absence of ketosis, and glycemic control without insulin for a minimum of at least 2 years. They also demonstrated an autosomal dominant inheritance (27). Since its recognition, reports confirm the existence of such youth onset DM which if different from the insulin dependent DM. The prevalence of this distinct form of DM also shows divergence between regions of the world.

Fibro Calculus Pancreatic Diabetes (FCPD)

Fibro calculus pancreatic diabetes (FCPD) is a rare but unique and unexplored type of DM found specifically in tropical countries including India, Indonesia, Bangladesh, Sri-Lanka, Brazil and a few African countries (28). FCPD was earlier called “tropical calcific pancreatitis (TCP)”. According to the American Diabetes Association (ADA) classification, DM originating secondary to any pancreatic origin is classified as type 3c DM. Chronic pancreatitis remains the most common etiology for the development of type 3c DM and chronic alcoholism in developed countries is a major cause of chronic pancreatitis contrasting with FCPD, which develops in the absence of alcohol intake.

FCPD is seen in the spectrum of DM associated with chronic pancreatitis and characterized by the presence of large calculi in the dilated pancreatic ducts along with significant fibrosis and atrophy of the gland. This leads to both exocrine and endocrine dysfunction. Population based studies of FCPD are scarce and the majority are reported from India. The

reported population prevalence of FCPD was 0.019% among all DM patients (29). FCPD prevalence has declined from 1.6% in 1991-1995 to 0.2% during 2006-2010 while the BMI in FCPD increased (30). Similarly, Balakrishnan et al (31) found that only 3.8% among type 3c DM patients have FCPD, making chronic idiopathic chronic pancreatitis as the major contributor. The prevalence is approximately15% in young patients referred to a tertiary center (32). The declining prevalence of FCPD is principally attributed to an improvement in nutritional status however the real cause remains to be determined.

GAPS AND CHALLENGES

Despite rising awareness of DM, the problem of ignorance about DM still exists. Data reveal the alarming fact that one in two adults with DM were ignorant about their condition. The majority of the undiagnosed cases occur in low- and middle-income countries. Likewise, the proportion of DM that is undiagnosed differs between regions. More than half of the patients living with DM in tropical regions like Africa and South-East Asia are undiagnosed while in European and North American countries the proportion undiagnosed is remarkably lower (IDF). Such high rates of undiagnosed cases reflect insufficient access to healthcare, poorer capacity of healthcare models, lack of pertinent diagnostic modalities, trained personnel, and inadequate patient health education. It should also be borne in mind that such remarkable levels of undiagnosed cases unquestionably impact morbidity and mortality because the later the diagnosis the higher the chances of disease complications. Additionally, people with a delayed diagnosis of DM, place an extra pressure on the healthcare structure due to higher complications (31).

Existing international guidelines for DM management are based on research conducted in developed countries. Extrapolating and applying such evidence to low- and middle-income countries may not be appropriate and requires a shift from being only developed country centric to more inclusive and international. Widespread effective patient awareness, modified affordable screening methods, appropriate diagnostic strategies, the need to diagnose people with DM earlier, and an increase in the coverage of preventive counselling is needed. In addition to diagnosing DM, efforts to diagnose complications earlier with non-invasive affordable screening tools could also improve outcomes (33,34). Lifestyle modification the most promising tool to prevent DM becomes the foremost inexpensive and best option in resource poor settings (35). DM takes a huge toll and is a major economic burden both to the individual as well as at the national level. The total DM related health expenditure has shown a steady rise over time, and this has been found to be lower in tropical regions as compared to temperate zones.

The North American and European regions display higher total DM related health expenditure while the tropical regions, despite having more than a third of the DM population are responsible for only one-tenth of the global DM related health expenditure. Along the same lines, DM becomes a major contributor to total health expenditure. In tropical regions like South America, Middle East, and North Africa expenditure due to DM contributes to almost one fifth of the total health expenditure while in Europe, DM expenditure as a proportion of total health expenditure is less than one-tenth. This can plausibly be explained by the fact that delayed diagnosis and greater chances of pre-existing complications result in higher expenditures. It is estimated that one third of all deaths from DM occur in the working age group which contributes to the economic burden. The Middle East and North Africa regions have the highest proportion of total deaths related to DM in the working age group. Similar challenges exist for T1DM as well with most developing countries reporting a very sub-optimal glycemic target achievement and control. Guidelines coordinating with existing government programs and primary care facilities aid in benefiting patients (36).

COMPLICATIONS

DM related mortality contributes to 12% of all-cause mortality in the 20-79 years age group. DM related morbidity also augments the economic burden of the disease globally. The microvascular and macrovascular complications of DM account for the majority of the morbidity & mortality. Although disease duration and glycemic control are important risk factors, ethnicity may also be a risk factor for complications.

Microvascular Complications

The prevalence of retinopathy varies between tropical countries. Indian studies report a prevalence ranging from 12-18% (37–39) which is lower than in Western cohorts. In contrast, data from Tanzania and other regions in Africa show a prevalence of 27-31% (70). In India, the prevalence of retinopathy at diagnosis was also strikingly lower among Indians with diabetes than seen in Western counterparts (40–43). Although duration of diabetes and glycemic control are consistent risk factors for retinopathy, diet patterns with increased antioxidants may serve as a probable protective factor (39).

Racial differences in the prevalence of diabetic nephropathy exist with Asian and African groups showing a higher nephropathy prevalence. Risk of end stage renal disease is higher in these populations than in Western populations (44). The prevalence of nephropathy ranges from 30-36% in various tropical regions (45,46) while one study from India reported a lower prevalence (47).

The prevalence of DM neuropathy is very heterogenous among different regions of the tropics. The prevalence estimates from Indian studies show lower figures in comparison to other tropical countries like Cuba, Mexico, Peru, and Caribbean countries (48–50). The different definitions used for DM neuropathy and characteristics of study populations may account for the differences in prevalence data. Asians when compared to Caucasians have a lower prevalence of neuropathy and possible explanations include lower smoking rates resulting in better peripheral vascularity and preserved skin micro-vascularization, and shorter height of Asians (increased height is a known risk factor for neuropathy).

Macrovascular Complications

Cardiovascular disease is the most common reason for mortality in people with DM. The pattern and prevalence vary between regions. The prevalence is less in tropical countries compared to Western countries, probably due to the relatively young population, lack of diagnostic facilities, and death due to other causes which prevail in most tropical countries (51). With Western countries now showing a progressive decrease in cardiovascular deaths, several tropical regions have reported a significant increase in cardiovascular mortality in recent decades (50,52). This could be attributable to the rampant Westernization with harmful transition in lifestyle increasing cardiovascular risk factors, growing population, and aging (53). Data from India show the susceptibility of Asian Indians to coronary artery disease. Asian Indians show early onset, more severe disease, and higher risk of mortality that Caucasians (54). DM by virtue of its insulin resistance and atherogenic dyslipidemia further aggravate this risk. On the contrary, peripheral vascular disease is comparatively rare among Indians. Younger age of onset of DM and lesser prevalence of smoking contributes to the decreased prevalence (55).

Diabetic Foot Ulcer & Tropical Diabetic Hand Syndrome

DM foot, a serious chronic complication of DM, shows an increasing prevalence worldwide owing to the rising DM prevalence and increased life expectancy. The prevalence of DM foot ulcer is heterogenous even between tropical regions with the Africa region showing higher caseloads than Asia and Australia.

Still the overall prevalence is greater in North America and the reason for such differences could be increased prevalence of smoking among Americans than South Asians or poor screening processes in tropical countries (56). One of the important risk factors for developing a foot ulcer is barefoot walking, which prevails in most communities in Africa and Asia. Other risk factors, which are peculiar to these populations, include utilizing inappropriate footwear, more susceptible to rodent bites during farming activities, etc. (57). It is also shown that the duration between DM onset and onset of foot ulceration is shorter probably due to late diagnosis of DM (58). The bacteriology of foot infections also depends on climatic conditions with gram negative organism showing higher prevalence in the tropical and sub-tropical regions. DM foot ulcers increase healthcare costs, risk of amputation, and mortality (59). In the tropical regions, native practices to treat DM foot ulcers with plant parts remain widespread even in the modern era.

Tropical DM hand syndrome (TDHS) is a comparatively less recognized complication than DM foot. Since its earliest description from Africa, many cases have been reported in Africa and India (60). It is distinct from the DM hand syndrome where the latter predominantly involves joints and skin, leading to limited mobility. TDHS usually follows a trivial trauma and involves cellulitis ultimately progressing to fulminant sepsis or gangrene. Early aggressive antibiotic therapy with or without surgical intervention is needed for adequate management (61).

Acute Complications

Hyperglycemic emergencies constitute an important cause of emergency presentation of T1DM as well as T2DM. Up to a maximum of 80% of T1DM patients present with diabetic ketoacidosis (DKA) at diagnosis and this varies between countries. It has been shown that countries with higher background prevalence of T1DM have lower frequency of DKA at presentation with Sweden showing the lowest frequency of DKA at presentation while the United Arab Emirates and Saudi Arabia show the highest frequency. The same study showed that the frequency of DKA at presentation progressively decreases with increasing latitude thereby demonstrating a higher risk in tropical countries (62). Heat exposure has been shown to be associated with hyperglycemic emergencies through various mechanisms such as reduced insulin activity in insulin preparations exposed to high ambient temperatures, higher environmental temperature leading to increased counter regulatory hormones, higher risk of dehydration, and decreased thermoregulatory activity in the elderly (99). Interestingly higher environmental temperature is also an important risk factor for hypoglycemia. Asian countries also report a higher frequency of DKA among T2DM than Western populations (63). The mortality rates are also comparatively higher in tropical countries (64). It is also important to note that FCPD despite beta cell destruction, does not commonly lead to DKA episodes (65).

Diabetes & Infections

Uncontrolled DM is a well-known risk factor for infections and poor outcomes, due to altered immune responses (97). For some infections, there is evidence that poor glycemic control correlates with infection risk as well as severity. The following mechanisms confer increased susceptibility to infections in people with DM:

(i) Altered skin flora and increased risk of breach in integrity due to neuropathy and angiopathy (66)
(ii) Altered gut microbiome (67)
(iii) Impaired neutrophil function (68)
(iv) Impaired function of macrophages, T-cells, and NK cells (69)
(iv) Endothelial dysfunction, oxidative stress (70)

Some infections like rhino cerebral mucormycosis, *Klebsiella pneumoniae* related liver abscess, emphysematous pyelonephritis or cholecystitis, and Fournier's gangrene are DM specific (71,72). Certain infections like candidiasis, bacterial pneumonia,

urinary tract infections, skin and soft tissue infections, and bloodstream infections, although not exclusive for patients with DM are more common and severe among people with DM (73,74).

The increasing incidence and prevalence of DM in the tropics add to the infectious disease load and severity in the tropics. Infections are an important cause of morbidity and mortality in people with DM. Tropical regions are home to endemic infections like tuberculosis, dengue, melioidosis, leishmaniasis, helminthic, and parasitic infections. Patients with DM are affected out of proportion by tuberculosis, malaria, and Human immunodeficiency virus (HIV). The plausible reason for a higher risk of infections in people with DM in the tropics include:

(i) higher possibility of DM being undiagnosed or the diagnosis delayed
(ii) poorly controlled DM due to suboptimal management
(iii) co-existing malnutrition and poor hygiene
(iv) reduced access to healthcare facilities & infection care

Therefore, the tropical countries face a double disease burden, persisting communicable diseases and DM worsening the communicable disease burden. While DM, a proven risk factor for infections, confers higher rates of infection with common bacterial organisms in high income countries in tropical countries, in addition to higher rates of common organisms, the risk of tropical infections poses additional concerns.

BACTERIAL INFECTIONS

Among bacterial infections, tuberculosis has a bidirectional relationship with DM. People with uncontrolled DM have a three times higher risk of developing active tuberculosis, more atypical presentation, higher rate of treatment failure, and recurrence (75). Conversely active tuberculosis leads to stress hyperglycemia (76). Recent reports also suggest the number of patients of tuberculosis with coexisting DM exceeds the number of TB-HIV coinfection (77). Among the top 10 countries harboring global tuberculosis cases, most of the countries also show a high prevalence of DM (78). Understanding the impact of DM on tuberculosis, some countries have implemented collaborative interventions to improve detection of DM among patients with tuberculosis by screening all TB cases for DM (78). In contrast, screening all patients with DM for TB, despite being very important, still has practical difficulty owing to the limitations of available screening tests.

Melioidosis, another important tropical disease, is caused by Burkholderia pseudomallei, a gram-negative bacterium. DM increases the risk of melioidosis, which is usually prevalent in rice farming countries such as South-East Asia (79). With the rising prevalence of DM in tropical countries along with the increasing life expectancy, the burden of melioidosis may prove disastrous. Contradictory evidence also exists with regards to the impact of sulfonylurea treatment on the immune effects against melioidosis (80). DM serves as an independent risk factor for severity of scrub typhus, a rickettsial disease in tropical regions (81).

VIRAL INFECTIONS

Viral infections of significance in the tropics include dengue, arbovirus, severe acute respiratory syndrome, Middle East respiratory syndrome virus, and Ebola virus. Dengue, a mosquito borne infection, has shown a relation with DM. DM is associated with more severe dengue-induced thrombocytopenia, dengue shock syndrome, and higher risk of acute kidney injury (82–84). Similar evidence of DM predisposing to more severe chikungunya, West Nile fever disease does exist although such evidence on zika virus is inadequate (85,86). Likewise, DM is an important risk factor for Middle East Respiratory Syndrome (MERS) and is associated with higher mortality among severe acute respiratory syndrome (SARS) virus (87,88). Hepatitis B virus (HBV) also shows a close association with DM. Its prevalence is

higher among people with DM, and DM is described to be associated with HBV disease progression. On the other hand, people with chronic HBV have an increased risk of developing DM. DM is more common among people living with HIV with data from tropical regions showing a more consistent and stronger association then those from high income countries (89,90). Advancements in retroviral therapy have transformed HIV infection from being associated with acquired immunodeficiency syndrome to a chronic disease associated with DM. The fact that DM in patients living with HIV develops at a much younger age than the general population is of great public health importance (61).

PARASITIC INFECTIONS

Malaria, caused by Plasmodium sp., is transmitted via mosquito bites. Africa accounts for the majority of cases. With co-existent increasing DM prevalence in Africa, a study from Ghana found that people with DM had a 46% increased risk of Plasmodium falciparum infection (91). Malaria infection during pregnancy is associated with intrauterine growth retardation, which in later life heightens the risk of insulin resistance and DM risk. DM is linked to an increased risk of leishmaniasis, whereas hyperglycemia was more common in patients with Chagas disease and cardiomyopathy than patients without cardiomyopathy (92,93). Interestingly a few helminthic infections like Schistosomiasis, round worm, and hook worm have a possible protective effect against DM (94).

FUNGAL INFECTIONS

Certain fungi are more frequent in the tropics than temperate regions due to the hotter and wetter conditions prevailing in the tropics. Fungal infections, typically the invasive ones, are also more common among immunocompromised individuals constituting opportunistic infections. Uncontrolled DM, a relatively immunocompromised state, and the climatic conditions of tropical regions favoring the prevalence of fungi, lead to fungal infections contributing importantly to the infection disease burden in the tropics. Mucormycosis caused by Zygomycetes, presents specifically as rhino-orbital-cerebral disease in people with DM. Although different forms of mucormycosis like pulmonary, gastrointestinal, and cutaneous types exist, rhino-orbital-cerebral mucormycosis is specifically associated with poorly controlled DM (95). Records from tropics show that among all patients with Mucormycosis, DM was seen in more than three-fourths of the patients. In the low-income countries, mortality due to mucormycosis is also higher than that in the developed countries owing to the shortcomings in medical and surgical management as well as poor glycemic control (96). Additionally, invasive aspergillus infections are also on the rise in the tropical regions.

FIBRO CALCULUS PANCREATIC DIABETES (FCPD)

Pathogenesis

The exact pathogenesis remains elusive. Factors like environmental toxins, nutrient deficiency, and genetic factors in combination may have a role.

(i) Environmental toxins: The most popular concept in the pathogenesis was the cassava hypothesis by McMillan and Geevarghese (4). Cassava contains cyanogenic glycosides. Cyanide detoxification in the body requires sulfur containing amino acids. In coexisting malnutrition, cyanide detoxification is impaired leading to pancreatic damage. Although cyanide ingestion in experiment rat models lead to transient hyperglycemia, permanent diabetes was not reported even with long term cassava consumption in rat models, thereby questioning this hypothesis (4). Geographic distribution of FCPD coincides with areas that consume cassava yet other areas where cassava consumption is not documented also have FCPD. The possible role of other cyanide containing foods such as jowar and sorghum may play a role.

(ii) Nutrient deficiency: The role of nutrient deficiency in the pathogenesis of FCPD has been a matter of debate. Nutrient deficiency could be the cause of as well as an effect of FCPD. Micronutrient deficiency and low vitamin C, vitamin E and beta carotene intake leading to oxidative stress may play a role in the etiology. Oxidative stress may also play a crucial role as evidenced by higher malondialdehyde levels and reduced antioxidant markers. Special interest with regards to selenium deficiency has been proposed. Western data showing that serum selenium levels were lower in those with chronic pancreatitis than in controls has kindled the hypothesis that lower selenium levels are associated with an accelerated course leading to DM in tropical pancreatitis. Yet a study comparing the selenium levels in healthy volunteers and patients with chronic pancreatitis in tropical and temperate regions did not confirm that selenium levels are involved in the DM that occurs in association with chronic pancreatitis (97).

(iii) Genetic factors: Studies have shown a familial aggregation, observed in up to one-tenth of cases (91) (98). Alterations in genes such as serum protease inhibitor Kazal type (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and chymotrypsinogen C have been highlighted in FCPD cases.

Overall, no one factor is responsible for the pathogenesis while probable involvement of multiple factors may explain the occurrence. The pathogenesis of DM includes defective insulin secretion as well as insulin resistance in FCPD. Deficiency of pancreatic polypeptide and storage of triglyceride in liver due to reduced fat store, contributes to insulin resistance (65).

Unfortunately, there is no specific etiology identified in FCPD despite several proposed theories. The initial explanation of cassava (tapioca) induced injury to the pancreatic acini through cyanide generation is flawed by the fact that not all with cassava intake develop the disease (6,7). A diet pattern of high carbohydrate and low protein is also implicated but the underlying mechanism is not known. Perhaps, genetic predisposition partly explains the FCPD etiology. A recent study has shown that 62.5 percent of FCPD patients harbor variation in the serine protease inhibitor Kazal type 1 (SPINK1) gene , particularly the N34S polymorphism (8). The role of other genes like PRSS1, PRSS2, CFTR, CTSB are not fully elucidated.

Apart from pancreatitis development, how diabetes develops is also not understood. Insulin deficiency and beta cell dysfunction are the primary pathology found. However, newer evidence suggests that altered glucagon dynamics, incretin abnormalities, and the presence of abnormal body composition leading to selective insulin resistance may contribute to the development of diabetes in FCPD (1,9) (99).

Clinical Features and Diagnosis of FCPD

The clinical features of FCPD are unique. The natural history usually progresses through three distinct stages. The initial period, where recurrent abdomen pain is the main clinical feature, often occurs in adolescents or early second decades. The second stage is characterized by classical exocrine pancreatic insufficiency with resultant steatorrhea symptoms. Steatorrhea is characterized by recurrent diarrhea with bulky, foul smelling, greasy stool, and predominant symptoms of fat malabsorption. Subsequently, fat related vitamin deficiency (A,D,E,K) features ensue. Other macro and micronutrients deficiencies are also present. In the third stage, that usually occurs in the late second to third decade, frank hyperglycemia occurs. FCPD patients are classically lean and malnourished. They have very brittle DM with high glycemic variability that is difficult to control.

Abdominal pain is conspicuously absent or less in intensity and frequency in the third stage, but the full-blown picture of both endocrine and exocrine deficiency persists. 50% of patients with FCPD without DM at baseline develop DM after 5 years of follow-up (100), mostly at the third decade, however the

percentage is even higher as age advances. The diagnostic criteria proposed by the Mohan et al encompasses all the clinical features described (See Table 1, Adapted from reference) (101). Despite a very high glucose, FCPD patients do not develop diabetic ketoacidosis (DKA). The reasons proposed are : 1) simultaneous destruction of pancreatic alpha cells leading to absence of glucagon which is a crucial hormone for ketogenesis in the liver. This is coupled with absence of absolute insulin deficiency in FCPD, as compared to T1DM, preventing lipolysis; 2) these patients are chronically malnourished and have very low free fatty acid reserve thus adequate substrate for ketone generation is usually absent and 3) carnitine deficiency as a part of generalized malnutrition as carnitine is required for the mitochondrial beta oxidation (28,101).

TABLE 1. DIAGNOSTIC CRITERIA FOR FCPD
1. Occurrence in a tropical country
2. Diabetes as per standard diagnostic criteria
3. Evidence of chronic pancreatitis: a. Pancreatic calculi on X-ray or b. At least 3 of the following: i. Abnormal pancreatic morphology by imaging ii. Chronic abdominal pain since childhood iii. Steatorrhea c. Abnormal pancreatic function test
4. Absence of other causes of pancreatitis like alcoholism, hyperparathyroidism, marked hypertriglyceridemia, hepatobiliary disease etc.

Table from the Endotext chapter entitled Fibrocalculus Pancreatic Diabetes

The diagnosis of FCPD is mostly clinical and supported by imaging. Since FCPD has an asymptomatic course when the pancreatic injury has happened and frank glycemia is not present, the diagnosis is often delayed and there is an unmet need for screening in such patients. The classical patient is a lean malnourished patient with severe hyperglycemia requiring multiple insulin doses. Abdominal imaging, particularly computed tomography (CT) scans are helpful to diagnose pancreatic pathology. The CT hallmark is 1) pancreatic duct dilation, 2) large pancreatic calculi involving the major ducts and 3) pancreatic atrophy and fibrosis. These features differ from alcoholic chronic pancreatitis where the pancreatic stones are smaller and have speckled pattern and involves smaller pancreatic ducts (101). However, other common causes of pancreatitis like alcohol, hyperparathyroidism, gallstones, and hypertriglyceridemia should be ruled out in such patients.

Despite having high glycemic variability and an elevated HbA1C, FCPD patients are at lower risk of micro and macrovascular complications compared to classical (T2DM). In a study from the Southern part of India it was shown that the prevalence of coronary artery disease, cerebrovascular stroke, and retinopathy was significantly higher in the T2DM patients compared to FCPD patients confirming this notion (102). This difference is possibly related to the absence of insulin resistance and other risk factors like obesity and dyslipidemia in FCPD patients, but further work is required to better understand this dichotomy. Nevertheless, all patients should undergo careful investigation for the routine micro and macrovascular complications. Periodontal disease is common in FCPD similar to that seen in T2DM and the severity correlates with poor glycemia (103). Hypoglycemia

unawareness is found in 73% of FCPD patients and classically is related to the lower fasting and post prandial glucagon levels in a subset of patients and contributes to the higher glycemic variability (104).

It is important to evaluate pancreatic exocrine insufficiency by fecal elastase estimation. However, fat malabsorptive features may be absent in tropical countries since the diet may be low in fat. Other abnormalities such as high triglycerides during hyperglycemia can be seen. Pancreatic amylase and lipase are not elevated in the chronic phase but may rise if an acute attack is present. Pancreatic carcinoma is a dreaded long-term complication of FCPD. Usually, pancreatic carcinoma develops much earlier, around the 5th decade in these patients and is diagnosed at an advanced stage (105). Unexplained weight loss and sudden deterioration in glycemic control along with abdominal pain distinct from the usual pancreatitis pain, warrants urgent investigation for pancreatic carcinoma (101).

Management and Challenges in FCPD

The mainstay of management of hyperglycemia is insulin. However, the doses may be quite variable and require frequent adjustment. Sometimes metformin and sulphonylureas are sufficient to control glycemia in milder cases. Lack of evidence of management of FCPD is a concern and should be addressed urgently. Incretin mimetics like DPP-4 inhibitors and GLP-1 analogues should be used cautiously if at all in FCPD. Ideally a closed loop system for continuous subcutaneous insulin delivery coupled with continuous glucose monitoring should be used whenever possible in FCPD patients but need further studies for this recommendation. Recent studies have shown the impact of SGLT-2 inhibitors in pancreatectomized patients, and hence they can be an important choice in FCPD patients, but one must be cautious about potential weight loss (106).

With documented exocrine pancreatic insufficiency in FCPD, pancreatic enzyme replacement therapy (PERT) may help improve glycemia and hence should be considered in patients with chronic pancreatitis (107). The usual dose is 10,000-25,000 lipase units and requires escalation to higher dose up to 50,000 per meal or less for snacks. The capsules should be spread throughout the meal to maximize the benefits. Usually, dietary fat restrictions are not advised but a high fiber diet may aggravate abdominal symptoms in FCPD, thus better avoided. Fat soluble vitamin replacement is necessary. Eventually some patients having refractory pain require either endoscopic or open surgical procedures for drainage. Unfortunately, there is no therapy to halt the progression from the pancreatitis phase to the FCPD phase, however antifibrotic treatment like pirfenidone has shown some effect in experimental preclinical studies (108).

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