

**DIABETES MELLITUS IN RELATION TO MEDICATION
ADHERENCE AND QUALITY OF LIFE**

Pathan Amanulla Khan*, B. B. Sarah Nousheen, Khateeja Sultana,
Mohd. Hussain Hyder, Hifsa Umama

Anwarul Uloom College of Pharmacy, Hyderabad, Telangana, India

Correspondence

Pathan Amanulla Khan

Department of Pharmacy Practice,
Anwarul Uloom College of Pharmacy,
Hyderabad-500001, Telangana, India
✉ aman.pathan811@gmail.com

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ABSTRACT

The World Health Organization (WHO) defines diabetes as a chronic disease caused by inherited or acquired deficiency in the production of insulin or by the ineffectiveness of insulin produced, causing hyperglycemia and further end organ damage. The terms 'diabetes' and 'mellitus' were coined by Aretaeus of Cappadocia and Willis. T respectively. Human insulin was discovered by Banting, Best and Collip in 1921-1922. This was followed by the discovery of oral hypoglycemic agents, which dramatically modified the existing management strategies of diabetes, aiding in improving overall patient well-being. However, despite these advancements, the disease is rapid in its growth, with an estimated global increase to 625 million cases by 2045; the prevalence in India, the second most diabetes populous country, is estimated to rise to 151 million by 2045. Major factors implicated in the disease burden include population aging, urbanization, and poor diet quality and lifestyle habits. Diabetes related mortality on the other hand, is influenced by poor medication adherence and failure to attend scheduled clinic appointments. Such rapid expansion of the disease can be curtailed by adopting preventive strategies with regard to diet and lifestyle and with early diagnosis and appropriate treatment. Additionally, for the purpose of assessing treatment and care, evaluation of medication adherence and quality of life are crucial. Therefore, this review is a modest attempt to furnish an overview of the factors affecting medication adherence and quality of life and the different scales and questionnaires utilized for the evaluation of the two.

INTRODUCTION

Diabetes mellitus, principally a metabolic disorder, is defined by the World Health Organization (WHO) as “a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves”.^[1]

The American Diabetes Association (ADA) defines diabetes as “a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels”.^[2]

HISTORY

The history of diabetes mellitus can be traced back to the Egyptians three millennia ago, who were the first to elucidate symptoms analogous to those of the disease.^[3] The term ‘diabetes’ (Greek, ‘siphon’) apparently originated and was coined in the first century A.D by Aretaeus of Cappadocia, although ancient literature makes little mention of this.

^[4] Sweetness of urine in diabetics was primarily reported by Avicenna and the primitive Indians.^[3,5] It was later rediscovered by Thomas Willis, who then introduced the term ‘mellitus’ (Latin, ‘honeyed or sweet’) in 1675.^[5]

While studying the anatomy of pancreas, Paul Langerhans in 1869, discovered pancreatic aggregates of cells. After a period of twenty four years, these were re-identified and named by Laguesse as the ‘islets of Langerhans’.^[6] The occurrence of diabetes in a pancreatic customized canid, discovered by von Merring and Minkowski in 1889, was sufficient evidence to trace the roots of diabetes.^[6,7] Sharpey-Schafer, an English physiologist, is well known for predicting the existence of insulin prior to its discovery. The term ‘insulin’ was introduced by de Meyer and Sharpey-Schafer in 1909-1910.^[8] From 1914 to 1916, Romanian physiologist, Nicolae C. Paulescu, injected pancreatic extracts (later named ‘pancreine’) into diseased dogs and normalized their glucose levels. However, no official publication was made regarding the discovery until 1921.^[9,10] It was in 1921-1922 that Banting, Best and Collip, discovered, and purified the hormone insulin suitable for human administration.^[3,6,8]

Following this tremendous breakthrough in the field of Diabetology, insulin began to be produced on a large scale. Oral antidiabetic drugs were subsequently discovered in the following order: sulfonylureas, biguanides, alpha glucosidase inhibitors, meglitinides, thiazolidinedione, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose linked transporter-2 (SGLT-2) inhibitors.^[8]

EPIDEMIOLOGY

Global scenario

In 1998, 60% of the global mortality (31.7 million) could be attributed to non-communicable diseases. Of these, heart diseases accounted for the majority of deaths, followed by diabetes mellitus in the fourth position.^[11] In 2018, the global mortality increased to 71% (41 million people), with heart diseases (17.9 million) being the leading cause of early NCD deaths annually, followed fourth by diabetes (1.6 million).^[12]

The global prevalence of diabetes mellitus, without regard to its types, was estimated to be 2.8%, equivalent to 171 million people in 2000,^[13] 8.5%, equivalent to 422 million people in 2014,^[14] 425 million people in 2017, and is projected to rise to 625 million people by 2045.^[15] Moreover, India (31.7

million) ranked first in the prevalence of diabetes in 2000, followed by China (20.8 million) and the US (17.7 million).^[13] In 2017, China took the lead with 114 million cases, followed by India (73 million) and the United States (30 million).^[15] The prevalence is higher in low- and middle-income countries, which account for 79% of the total diabetes cases^[14, 15] and three-fourths of the global NCD mortality.^[12] Diabetes affects more men than women,^[13, 14] with a majority of disease related deaths occurring under the age of 70 years.^[12, 14]

Indian scenario

In India, as per the Indian Council of Medical Research, Public Health Foundation of India, Institute for Health Metrics and Evaluation, non-communicable diseases accounted for 37.9% of the total mortality in 1990, which increased to 61.8% in 2016. Cardiovascular diseases are the leading cause of death while diabetes ranks fourth among all the NCDs.^[16] In 2017, the prevalence of diabetes mellitus was estimated to be 8.8%, equivalent to 72 million people, expected to rise to 151 million people by 2045.^[17] Males portrayed a higher prevalence than females, with a majority of cases above the age of 18 years.^[16]

CLASSIFICATION ^[18]

The American Diabetes Association (ADA) classifies diabetes mellitus into four distinct types:

1. Type 1 diabetes (due to self-destruction of β cell mass)
 - i) Immune-mediated (constitutes 5-10% cases of diabetes)
 - ii) Idiopathic diabetes (fairly rare, constitutes a small proportion of cases)
2. Type 2 diabetes (due to insulin resistance; constitutes 90-95% of the diabetes cases)
3. Gestational diabetes mellitus (during pregnancy)
4. Other specific types of diabetes
 - i) Monogenic diabetes syndromes (account for <5% of diabetic cases)
 - a. Neonatal diabetes (diagnosed in infants <6 months of age)
 - b. Maturity-Onset Diabetes of the Young (diagnosed in persons <25 years of age)
 - ii) Cystic fibrosis-related diabetes (occurs in 40-50% of adults with cystic fibrosis)
 - iii) Drug or chemical induced diabetes

RISK FACTORS ^[19]

These can be classified into biological, psychosocial and behavioral risk factors.

1. **Biological risk factors** which increase the risk of diabetes include a higher body mass index (BMI), increased distribution of body fat, metabolic syndrome, a higher testosterone-oestrogen ratio, dysregulation of adiponectin, occurrence of prediabetes and gestational diabetes mellitus (GDM). Higher brown adipose tissue (BAT) on the other hand, lowers the risk of diabetes mellitus.
2. **Psychosocial risk factors** include socioeconomic status, psychosocial stress, sleep deprivation and work stress. While the former is inversely associated with diabetes mellitus, the latter three directly impact the disease.
3. **Behavioral risk factors:** Consumption of sugar sweetened beverages and alcohol, and smoking increase the risk of diabetes. Adoption of a healthy lifestyle positively influences the overall well-being of an individual.

CLINICAL FEATURES ^[20]

Diabetes mellitus manifests with classic clinical symptoms such as polyuria, polydipsia and polyphagia. Other symptoms include frequent fatigue, blurred vision, paraesthesia, unexplained weight loss and delayed healing. Weight loss is more common in type 1 diabetics, while acanthosis

nigricans is frequently observed in type 2 diabetes patients. Gestational diabetes presents with no peculiar signs, hence screening is crucial during pregnancy.

PATHOGENESIS ^[21]

A number of factors i.e. genetic and environmental, such as obesity, hypertension and sedentary lifestyle have been implicated in the pathogenesis of type 2 diabetes mellitus.

DIAGNOSIS ^[18]

The American Diabetes Association (ADA) recommends fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) as standard tests for screening for diabetes. (See http://care.diabetesjournals.org/content/diaca-re/41/Supplement_1/S13.full.pdf)

WHY THE GLOBAL EPIDEMIC?

Globally, 425 million people were diagnosed with diabetes in 2017, estimated to increase to 625 million by 2045. Also, 6 million deaths could be attributable to the disease in 2017. ^[15] India reported 72 million diabetes related morbidities in 2017, estimated to rise to 151 million by 2045. ^[17] With such rapid an expansion of the 'Diabetes Empire', it is soon

to conquer every part of the world and become the largest epidemic in human history. Population aging, urbanization, physical inactivity, increased caloric intake, consumption of high glycemic index (GI) foods and obesity are the major factors driving the disease growth. ^[22] Diabetes related mortality on the other hand, is influenced by factors such as poor medication adherence and failure to attend.

Scheduled clinic appointments. Non-adherence and non-attendance deteriorate a patient's quality of life (QoL), eventually culminating in death of the individual. ^[23] Therefore, for the purpose of assessing treatment and care, it is crucial to comprehend the concepts of medication adherence and quality of life of patients.

MEDICATION ADHERENCE

Medication adherence is defined by the World Health Organization (WHO) as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider." ^[24]

Figure 1 diagrammatically represents the causes and the pathogenesis of T2DM.

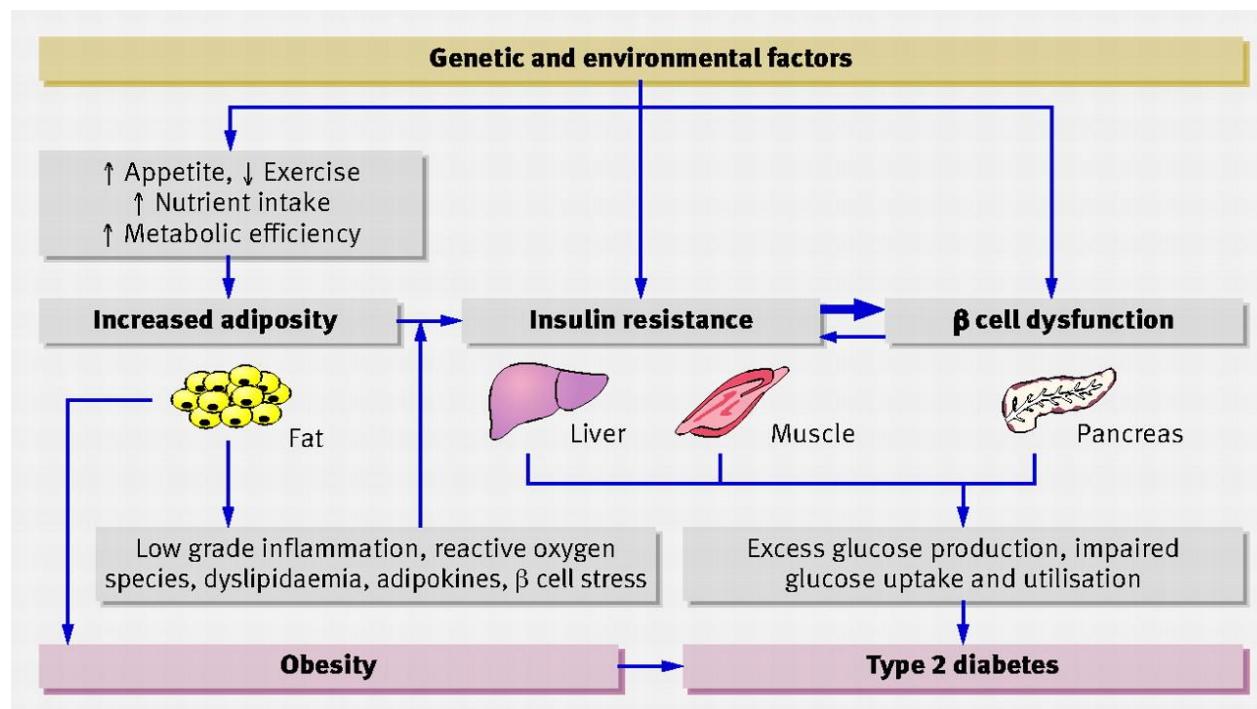


Fig. 1 Pathogenesis of type 2 diabetes mellitus

Factors affecting medication adherence

Poor medication adherence has been identified as a crucial factor contributing to the diabetes burden in India. Non-adherence is very common a factor which results in failure to achieve adequate glucose levels, failure to manage complications, increased admissions in hospitals and therefore a rise in disease related morbidity and mortality. [25]

Factors commonly influencing poor medication adherence in T2DM patients include:

- **Age and gender:** Patients above 60 years and females were found to be more

adherent to their medications when compared to the middle aged individuals and males. Elderly patients, being free from household and job responsibilities, are found to be very vigilant about their health. As a result good compliance to their prescribed medications was seen. Females follow a comparatively healthier life style, hence better adherence. [26]

- **Physical activity and diet:** Poor nutrition and sedentary lifestyle have been associated with low medication adherence. [27]
- **Smoking and alcohol consumption:** Forgetfulness was found to be an element

for poor medication adherence in smokers and alcoholic patients. [28]

- **Literacy:** Illiterate patients lack knowledge regarding diet, exercise and medications prescribed to them resulting in non-adherence. [29]
- Occurrence of adverse effects, intricacy of regimen, time required to reach hospital and low periodic wage directly impact the medication adherence of patients. [30]
- **Duration of diabetes:** Better medication adherence has been observed in patients recently diagnosed with diabetes, but as months and years pass by, compliance to anti-diabetic drugs decreases drastically. [31]
- **High income and depressive symptoms:**
 - Adults with a higher income generally experience greater work load, and depressive behavior and hence should be counselled more frequently about importance of prescribed medications. [32]
 - Short memory, inaccessibility of some anti-diabetic drugs, lack of communication between patient and provider, distrust in the provider, worry and reluctance are all negatively associated with medication adherence. [26,29]

Common scales and questionnaires used to assess medication adherence

Scales that are commonly used to assess medication adherence in patients with type 2 diabetes mellitus are the following:

- 1) Brief medication questionnaires
- 2) Eight-Item Morisky Medication Adherence Scale (MMAS-8)
- 3) The Self-Efficacy for Appropriate Medication Use Scale (SEAMS) [33]
- 4) 4-item Morisky Medication Adherence Scale (MMAS-4) [34]
- 5) Drug Attitude Inventory (DAI)
- 6) Medication Adherence Rating Scale (MARS)
- 7) Clinician Rating Scale (CRS)
- 8) Brief Adherence Rating Scale (BARS) [35]

Significance of assessing medication adherence [36]

Chronic disorders such as diabetes, hypertension, renal and cardiovascular disorders mandate high adherence to medications for improvement in the disease. Evaluation of medication adherence helps to predict the factors associated with non-adherence and analyze strategies to improve health outcomes of patients. It is therefore, an important measure for both clinicians as well as patients.

QUALITY OF LIFE (QoL)

In 1948, the World Health Organization (WHO) defined health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. There has been no amendment to the definition ever since. [37]

The WHO describes Quality of Life as “an individual’s perception of their position in life in the contest of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological states, personal beliefs, social relationships and their relationship to salient features of their environment”. [38]

Factors affecting quality of life

These can be grouped into four categories, i.e. factors related to the disease, those related to diet and lifestyle, psychological factors and therapy related factors. [39,40]

i) Factors related to the disease

a) Presence of complications (retinopathy, nephropathy and neuropathy) restrain the individual from being physically active, alter psychological status and deteriorate the patient’s quality of life. [39,40]

b) Comorbidities such as hypertension worsen the pre-existing condition, thereby deteriorating the QoL. [39]

c) Long standing disease and insulin use independently impact the QoL. With prolonged duration of the disease, there is progressive destruction of β -cells, poor glycemic control, thus worsening QoL. [39]

ii) Diet and lifestyle

Consumption of a healthy diet, designing a routine exercise program and maintenance of a healthy BMI have been associated with a better quality of life. [40] A diet rich in red meat has an inverse relation with the quality of life. [39]

iii) Psychological factors

Psychiatric disorders such as depression, anxiety and worry are negatively correlated with quality of life. [39,40]

iv) Treatment regimen

With advancement in the therapeutic regimen of the patient, the quality of life tends to decrease, attributable to an increase in worry related to diabetes. [40]

Common scales and questionnaires used to assess quality of life

Scales that are commonly used to assess quality of life in patients with type 2 diabetes mellitus include the following:

- 1) World Health Organization Quality of Life (WHOQOL-100)
- 2) World Health Organization Quality of Life-BREF (WHOQOL-BREF) ^[38]
- 3) Short Form Health Survey (SF-36) ^[41]
- 4) Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ) ^[42]
- 5) Audit of Diabetes Dependent Quality of Life (addqol) ^[43]
- 6) Diabetes quality of life (dqol) ^[44]
- 7) Revised Diabetes Quality of Life Instrument (dqol) ^[45]

Significance of assessing quality of life ^[46]

Quality of life instruments evaluate patient's perception of the disease, and identify the domain of life that has significantly been affected due to an existing illness. These are individualized approaches which determine the patient's level of satisfaction and impact of the disease on routine life. It is crucial that, aside from the conventional focus on clinical data of a patient, subjective measures such as a person's feelings be taken into account. Assessment of these measures therefore constitutes an important aspect of health care.

CONCLUSION

Diabetes mellitus is a chronic disorder affecting millions of individuals throughout the globe. With such rapid increase, it is soon to become the largest epidemic in human

history. The two main factors implicated in diabetes related morbidity and mortality include medication adherence and quality of life. Factors affecting adherence and quality of life are almost analogous. There is urgent need to address these factors to reduce the global diabetes burden.

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