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CLASSIFICATION OF DIABETES MELLITUS: WHY THE FLUX – A REVIEW

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ABSTRACT

Diabetes Mellitus (DM) is an endocrine and metabolic syndrome of various a etiology, characterized by chronic hyperglycaemia, symptoms, signs and complications. The classification of DM has been under a state of flux since 1965.[1-4] The 2019 Classification by the World Health Organization (WHO) includes two new types: 'Hybrid Types of Diabetes' and 'Unclassified Diabetes'.[5-6]

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HISTORY OF DIABETES MELLITUS

The word diabetes is derived from the Greek word that signifies a syphon. This draws attention to the increased urine (Polyuria) and thirst (Polydipsia). This description is over 2000 years ago. Aretaus the Cappadocian used the word 'diabetes' in the 2nd Century A.D. to describe Polyuria with associated thirst and emaciation as features of the fatal disease.[7-8] In the 5th Century Susrutha in India referred to DM as 'Honey Urine', while Willis in 1679 wrote that 'those laboring under this disease piss a great deal more than they drink'. The urine is wonderfully sweet as if it were imbued with honey or sugar.[7-8]

Later in 1815, the famous French Chemist Chereul discovered that the sugar in diabetic urine was glucose.[7] Claude Bennard in the 1850s described the internal secretions of glucose into the blood from its storage - 'glycogen' – in the liver.[8] In 1889 Minkowski and Von Mering showed that complete pancreatectomy in dogs resulted in a condition corresponding to severe DM in man.[8] The novel research of Banting and Best in 1921 in preparing insulin in a form effective in overcoming experimental diabetes in pancreatectomizied dogs marked the beginning of the era of modern diabetes therapy.[9-10] Since then, knowledge has increased on the diagnosis, epidemiology, aetiopathogenesis and management of DM. The production of insulin in commercial quantity has been possible through recombinant DNA technology.

CLASSIFICATION

The historical description of diabetes date from ancient times as already described. In 1965 the WHO published her first expert committee report on diabetes.[1] Type 1 was classified as insulin dependent diabetes mellitus, while 2 was called non-insulin dependent diabetes mellitus. We now know that Type 2 patients need insulin in emergency, or as beta-cell function detoriates with time.

The 1985 WHO classification recognized Malnutrition Related Diabetes Mellitus (MRDM) as a distinct entity with specific clinicopathological characteristics.[3] Malnutrition Related Diabetes Mellitus MRDM was found mostly in tropical countries. However, its incidence has declined over the years. Malnutrition Related Diabetes Mellitus MRDM is no longer recognized as a definite class in the WHO 2019 classification.[5] The 1999 WHO Classification dropped MRDM for lack of evidence as a specific class.[4] Hyperglycaemia first detected during pregnancy is either diabetes in pregnancy or Gestational Diabetes Mellitus (GDM). Known Type 1 DM and Type 2 DM is diabetes in pregnancy. Unknown cases with FPG ≥ 7.0 mmol/L or 2-hour post load plasma ≥ 11.1 mmol/L or HbA1c ≥ 48 mmol/mol is diabetes in pregnancy. For GDM: FPG 5.1 to 6.9 mmol/L or 1hour post load plasma glucose ≥ 10.0 mmol/L or 2hour post load plasma glucose 8.5 to 11.0 mmol/L. **Table 1** shows WHO 2019 Classification of DM.

PATHOGENESIS

Pancreatic B-cell dysfunction or destruction are common aetiological abnormalities in all forms of diabetes mellitus.[11-14] Different types of DM have different aetiology, pathogenic mechanism, natural history and treatment modality. The classification used should help guide clinical care decisions, stimulate research into aetiopathogenesis, and provide basis for epidemiological studies.

B-cell function can be measured by: C-peptide estimation, islet cell specific autoantibodies, markers of low grade inflammation, measure of insulin resistance, and assay of B-cell mass.[12] C-peptide can be measured in the urine or plasma. This could be in the fasting state or after stimulation, for example with intravenous glucagon. Autoantibodies against various B-cell components could be measured – Glutamic Acid Decarboxylase (GAD 65), Islet Antigen 2 (IA-2), Zinc Transporter 8 (ZnT8) and insulin.[15]

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TYPE 1 DIABETES MELLITUS (Type 1DM).

Susceptibility to Type 1DM has been linked to certain Human Lymphocyte Antigen (HLA) alleles in the Major Histocompatibility Complex (MHC), which controls immune-molecules located in plasma membrane of cells, C_2 and C_4 components of the classical complement pathway and properdin factor of the alternate complement pathway.[16-17]

Over 90% of Caucasian Type 1DM have either D3-DR3 or D4-DR4 antigen, while about 55-60% have both DR3 and DR4 alleles.[18-19] This HLA pattern was not found in few Nigerian studies.[20-21] This may explain in part the low incidence of Type 1DM in Nigeria. The onset of Type 1DM has been found to coincide or follow infection with mumps, rubella, cytomegalovirus, measles, influenza, encephalitis, poliomyelitis and Epstein-Barr virus.[22-23] Infection is also commoner during winter.[23]

TYPE 2 DIABETES MELLITUS (Type 2DM).

The concordance rate of Type 2DM among identical twins is 100%.[24-26] This suggests a strong genetic predisposition and association which has not been elucidated or worked out. Insulin resistance is a major pathogenic feature of Type 2DM; with delayed, inappropriate or sluggish insulin response to various physiological stimuli.[3] The serum insulin level is normal or high, with associated counter-regulatory hormone excess, for example glucagon.[13-15]

Obesity and other components of the metabolic syndrome are risk factors for Type 2DM.[5,15,24] The incidence and prevalence of Type 2DM are lower in communities involved in more physical exercise and activities than in those that are sedentary.[27] Exercise improves well-being, reduces body weight and improves insulin action.[28] Cases of mostly Type 2DM following infectious hepatitis has been documented in Nigeria.[29-30] However, the genetic component or susceptibility are not known. Use of indigenous spirits [31-32] and herbal medicines [33-35] have been associated with Type 2DM.

MONOGENIC DIABETES

This is usually due to single gene defect of B-cell function or single gene defect in insulin action. Through genetic testing and analysis many new cases of this type of diabetes have been described and characterized. Examples are shown in **Table 2.** This is one of the subtypes under other specific types. The other subtypes in the same group with monogenic diabetes are diseases of the exocrine pancreas, endocrine disorders, drug or chemical induced, infection related, uncommon specific forms of immune-mediated diabetes and genetic syndromes sometimes associated with diabetes mellitus.

HYBRID FORMS OF DIABETES

This describes two sub-types of diabetes mellitus. One is slowly evolving immune-mediated diabetes of adults, previously called latent autoimmune diabetes of adults. The second is called, Ketosis prone Type2 Diabetes. This group presents with Ketosis and insulin deficiency but later do not require insulin.

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TABLE 1: TYPES OF DIABETES MELLITUS (WHO 2019 CLASSIFICATION)

S/no	TYPE	FEATURES AND CAUSES
1.	**Type 1**	
2.	**Type 2**	
3.	**Hybrid forms of diabetes** a. Slowly evolving immune-mediated Diabetes of adults b. Ketosis prone Type 2 diabetes	Previously called Latent autoimmune diabetes of adults (LADA). Features of metabolic syndrome, a single GAD autoantibody & retains greater B-cell function Presents with ketosis and insulin deficiency but later does not require insulin: episodes of ketosis, not immune mediated
4.	**OTHER SPECIFIC TYPES** Monogenic Diabetes a. Monogenic defects of B-cell function b. Monogenic defects in insulin action **Diseases of the exocrine pancreas** Endocrine Disorders **Drug or chemical induced** Infection related diabetes **Uncommon specific forms of immune-mediated diabetes** Other genetic syndromes sometimes associated with DM	 **Trauma, tumour, Fibrocalculous pancreatopathy, Cystic fibrosis, Haemochromatosis, Pancreatitis, pancreatectomy** Cushing's syndrome, Acromegaly, Hyperthyroidism **Glucocorticoids, Thyroid hormone, Thiazides, Adrenergic agonists, Interferon-alpha, Nicotinic acid, Dilantin, Pyrinuron** Some viruses cause direct B-cell destruction **Associated with rare immune mediated diseases: Stiff man syndrome, anti-insulin receptor antibodies, insulin autoimmune syndrome (autoantibodies to insulin)** Down syndrome, Friedreich's ataxia, Huntington's chorea, Klinefelter's syndrome, Turner's syndrome, Porphyria
5.	Unclassified	New types of diabetes
6.	Hyperglycaemia first detected in pregnancy a. Diabetes Mellitus in pregnancy b. Gestational Diabetes Mellitus	

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TABLE 2 MONOGENIC DIABETES (WHO 2019 CLASSIFICATION OF DIABETES MELLITUS)

S/no	DEFECTS IN B-CELL FUNCTION: mutated gene followed by clinical syndrome	DEFECTS IN INSULIN ACTION: mutated gene followed by clinical syndrome
1.	GCK MODY	ISNR Type 1 insulin resistance
2.	HNF 1A MODY	INSR Leprechaunism
3.	HNF 4A MODY	INSR Rabson-Mendenhall syndrome
4.	HNF 1B RCAD	LMNA FPLD
5.	mt DNA32 43 MIDD	PP ARG FPLD
6.	KCN J11 PNDM	AG PAT2 CGL
7.	KCN J11 DEND	BSCL2 CGL
8.	69 24 TNDM	
9.	ABCC8 MODY	
10.	INS PNDM	
11.	WFS 1 Wolfram syndrome	
12.	FOXP3 IPEX syndrome	
13.	EIF2AK3 Wolcott-Rallison syndrome	
14.	Abbreviations: MODY = Maturity Onset Diabetes of young RCAD = Renal Cysts and Diabetes MIDD = Maternally inherited Diabetes & Deafness PNDM = Permanent Neonatal Diabetes Mellitus TNDM = Transient Neonatal Diabetes Mellitus DEND = Developmental Delay Epilepsy & Neonatal Diabetes	Abbreviations: FPLD = Familial Partial Lipodystrophy CGL = Congenital Generalized Lipodystrophy

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CONCLUSION

The use of genotyping, autoantibody studies, and the estimation of B-cell mass and function helps in the classification of diabetes mellitus. Some diabetic cases are unclassified especially at diagnosis and needs to be investigated further.

KEY WORDS: Hybrid forms of Diabetes, Monogenic Diabetes, Unclassified Diabetes, Hyperglycaemia in Pregnancy, Classification, World Health Organization.

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