The Evolving Face of Diabetes

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"Diabetes is a remarkable affliction, not very frequent among men… for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts… The patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst, unquenchable; excessive drinking, which, however, is dispro- portionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouth becomes parched and their body dry; the viscera seems as if scorched up; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire. They thirst, as if scorched up with fire …, and the emaciation is dreadful; nor does any great portion of the drink get into the system, and many parts of the flesh pass out along with the urine"[1]

Aretaeus of Cappadoccia 130 BC

Although recognised for millennia, it is likely that the cachectic, polyuric and wasting form of diabetes described by ancient physicians was type 1 diabetes, in extremis. In the modern times, the overwhelming majority of diabetes is type 2 diabetes, with global numbers in hundreds of millions. Pakistan, with a diabetic population of 33 million, is now ranked third among the countries with the highest number of patients with diabetes in the world.[2]

Formal accounts of type 2 diabetes are hard to find in historical texts, probably because for most part of history, this form of diabetes, with its gradual onset and measured pace, wasn't considered a disease. The term "diabete gras" or fatty diabetes, was coined by Lancereaux,[3] a French pathologist, in 1880, but this did not become a clinically recognised entity until the first half of the 20th century. One of the earliest clinical accounts of what we today know as type 2 diabetes can be credited to Elliot Joslin, in his 1916 monograph "The Treatment Of Diabetes Mellitus With Observations Upon The Disease Based Upon Thirteen Hundred Cases" which he described the diet and lifestyle changes which are even today the core principles of management.[4] Even then, the diagnosis of diabetes was very different from today, and indeed a large number of people who are diagnosed with diabetes today would be considered normoglycaemic by the standards of mid-20th century. Diabetes, for the vast majority of physicians, was only about raised blood glucose, which left untreated, led to complications in kidneys, eyes and nerves. The primary treatment target was glycaemic control, and the main drugs in the diabetes armoury were insulin, and insulin secretagogues like sulfonylureas. The role of insulin resistance in the pathogenesis of type 2 diabetes gained recognition in the latter half of the 20th century,[5] leading to the development of drugs which targeted insulin resistance. This led to the development of metformin in the 70's, and the thiozolidinediones in the late 90's, drugs which addressed the core problem of insulin resistance, rather than merely treating the symptom, vis hyperglycaemia. Around the turn of the century, came the appreciation that type 2 diabetes is not a disease which occurs in isolation, but usually overlaps with central obesity, hypertension and coronary heart disease. This led to the concept of the "syndrome X", later renamed the metabolic syndrome, a co-existence of cardiovascular risk factors including central obesity, hypertension, dyslipidaemia and hyperglycaemia.[6] Diabetes was now a disease of the cardiologist as much as that of an endocrinologist. More and more previously distinct conditions are now coming within the ambit of diabetes, making it truly a cross-disciplinary disease. A striking example is our new understanding of the link between type 2

diabetes, non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS), which were previously the sovereign domain of endocrinologists, hepatologists and gynaecologists separately. It is now recognised that the single theme which underpins all three is insulin resistance, and the manifestation of either multiple cysts in the ovaries or hepatic steatosis, is but a consequence of this underlying pathology. This has led to the American Diabetes Association recent recommendation for screening for hepatic fibrosis in all patients with type 2 diabetes[7]. Indeed, it is increasingly being recognised that the nomenclature of these conditions needs to be revised to reflect the critical role of diabetes and obesity in their pathogenesis. Nonalcoholic fatty liver disease has now been renamed metabolic dysfunction-associated steatotic liver disease (MASLD),[8] and it is proposed that PCOS should be renamed to multisystem reproductive metabolic syndrome.[9,10]

This paradigm shift in how we approach these diseases is also reflected in the current treatment strategies, with antidiabetic medicines standing shoulder to shoulder with the conventional system focused therapies. Furthermore, this has also led to an emphasis on developing diabetes drugs with advantages beyond mere glucose lowering. Medicines like sulfonylureas, meglitinides, and to some extent, dipeptidyl peptidase inhibitors, which have primarily glycaemic roles, are now being increasingly replaced with SGLT2 inhibitors and GLP1 agonists, which have shown to be potent agents with benefits which encompass not only diabetes but also chronic kidney disease, NAFLD and heart failure.

It is certain that the face of diabetes will keep on evolving, but one thing is becoming clear: diabetes is not just raised sugar in the blood. Our new understanding pictures diabetes as a continuum, with a considerable part of its journey undertaken before overt hyperglycaemia. A new nomenclature has been proposed for type 2 diabetes: dysglycaemia based chronic disease, or DBCD, with four stages. In this classification, Stage 1 is only marked by insulin resistance, manifesting as clinical stigmata including central obesity and acanthosis nigricans, and measurable by tests such as hyperinsulinaemic euglycaemic clamp or HOMA-IR. Stage 2 refers to non-diabetic range hyperglycaemia, presently known as prediabetes. Stage 3 marks what we currently call diabetes, with diabetic range values of fasting and post glucose hyperglycaemia. Stage 4 is the stage of vascular complications of diabetes.[11]

In conclusion, our growing understanding of diabetes as a multifarious condition with labyrinthine interactions with other metabolic disorders has completely transformed our management strategies. Two thousand years after Aretaeus first described diabetes in such graphic detail, we can truly say that diabetes is not merely a state of hyperglycaemia with osmotic symptoms. It is a more fundamental derangement in the body's milieu, with insulin resistance at its core, and like a hydra, it has many faces, and many tentacles which reach into every organ system in the body. The only way one can manage such a multifaceted condition is by adopting a multidisciplinary approach to target all its protean manifestations.

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