Volume 1 • Issue 1 • 2018

Scientia Ricerca

Editorial

Archives of Endocrinology and Diabetes Care

ISSN: 2579-017X

Novel Subgroups of Adult-onset Diabetes and its Complications

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Received: March 12, 2018; **Published:** March 14, 2018

Volume 1 Issue 1 March 2018

Incidence of Type-2 diabetes mellitus has more than doubled worldwide in the last two decades [1-4]. Swedish researchers stratified newly diagnosed patients into five subgroups using data driven cluster analysis based on six variables; glutamate decarboxylase antibodies, age at diagnosis, Body Mass Index, HBA1c, and homeostatic model assessment 2 estimate of Beta-cell function and insulin resistance [6]. Outcome analysis showed that those in cluster 3 had higher diabetic kidney disease, and those in cluster 2 had higher retinopathy. Currently, last four clusters are clubbed under type-2 diabetes. Some leading endocrinologists question the significance of this stratification, the cost involved in stratifying large diabetic populations and the usefulness of such classification in the management of the progression of the disease. Some are of the opinion that it might be possible to further refine the stratification based on biomarkers, genotypes and genetic risk scores. On the other hand, few researchers believe that it is too simplistic and may not add any value for the management of adult-onset diabetes.

American College of Physicians (ACP), in an evidence-based guidance statement have suggested that HBA1c between 7%-8% is okay for most type-2 diabetic patients. Some leading Endocrinologists from India feel that this ACP guidelines are not applicable for the Indian diabetics. These new guidelines by ACP has initiated a serious debate as to what should be the ideal normal value of HBA1c. American Diabetes Association (ADA) and American Association of Clinical Endocrinologists do not agree with the higher glycemic control targets recommended by the ACP. Majority of clinicians still feel comfortable with the old guidelines and prefer to keep the level of HBA1c between 6.5 to 7.0 in younger adults. Moreover, current literature on this topic is ambiguous regarding the benefits of tight glycemic control, which may be at times harmful, costly and hard to achieve. Diabetes care worldwide to a large extent, is centered around management of hyperglycemia by monitoring blood glucose levels using the gold standards, such as fasting glucose (> 120 mg/dl), HBA1c (6.5 to 7%) or post-prandial glucose (PPG; I-hour or 2-hour PPG levels). Currently, we are validating the Flash Glucose Monitoring (FMG) System (Ambulance Glucose Monitor AGM), Freestyle Libre (Abbott). Assuming that the interstitial tissue glucose profiles correlate with the blood glucose levels, we would like design our strategies to customize the treatment to target the tissue glucose peaks.

Excess weight, obesity and diabetes are in the increase worldwide and no country has been able to reverse the incidence of these chronic metabolic diseases. It is high time we make serious attempts, develop novel strategies to prevent or reduce the incidence of these diseases. Since I have been asked to write this editorial for the Journal of Archives of Endocrinology and Diabetes Care, I would like to offer a few suggestions as to what the future direction should be for the better management of adult-onset diabetes. As I have expressed many a times in my editorials and overviews, we will be in a better position to manage a disease, if we understand the factors that initiate or promote the pathophysiology of a disease. For instance, diabetes is managed worldwide by simply managing the blood sugar. There is very little known about how excess sugar levels in blood modify the physiology and function of blood cells or the components of the vessel wall. What all

proteins are glycated and how glycosylation of proteins affects the cardiovascular pathophysiology? Diabetics are supposed to have diffused atherosclerosis of the vessels. The reasons for this diffused atherosclerosis is not very clear. Atherosclerosis is considered a chronic inflammatory disease. However, general treatment protocols do not include any anti-inflammatory drugs. A better understanding of the mechanism involved in the development of various diabetes-related complications will help the clinicians develop better management protocols.

For instance, the cluster analysis studies of the Swedish investigators showed that those who were stratified under cluster 3 had higher incidence of diabetic kidney disease, whereas those under cluster 2 had significantly higher incidence of diabetic retinopathy. It would be really valuable if one can do gene profiling, and gene expression in subgroups of diabetics identified with the manifestation of various known clinical pathologies, such as retinopathy, neuropathy, nephropathy and vasculopathies, to determine what micro RNAs or what gene expressions modulate or promote these clinical complications of diabetes. In a bilateral collaborative study between the USA and India, that I am participating, we are studying the influence of maternal exosomes on the fetal growth and metabolism. Studies at the Children's Memorial Hospital, Washington DC have demonstrated a relationship between adipocyte-derived exosomal miRNAs and obesity-related diseases [6]. In other words, in individuals with obese adipocytes, fat cells change and begin to release different exosomes than the lean adipose cells do. One can do similar studies with individuals with pregnancy-induced diabetes to determine whether they too shed exosomes that regulate gene expression in the growing fetus and change its sugar metabolism. I hope the new journal, Archives of Endocrinology and Diabetes Care will provide a platform to endocrinologists and diabetologists to discuss these and many other important unanswered questions and develop novel methodologies for the management of various subgroups of diabetes.

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