

Newer molecular insights into type-2 diabetes mellitus

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Abstract

Beta cell function Type-2 diabetes mellitus (T2DM) has always been considered a heterogeneous and broad-spectrum disease with many associated complications and variations. Worthwhile in this regard were the findings that different individuals with T2DM label had slightly different set of clinical features and end-organ damage. Evidence is also there that pharmacotherapy related response also varies between individuals for the same category "T2DM". This report uses the existing molecular evidence to provide a suggested sub-classification for T2DM by using newly available molecular evidences from literature. The study broadly categorizes these T2DM with patients having primarily beta cell dysfunction or insulin resistance. While common features exists between T2DM subjects like hyperglycaemia and various organ damages, still the literature search highlight the subtle difference between the aforementioned two categories. Patients with insulin resistance can be clustered into obese, lipid/liver type and lipodystrophy associated features. Similarly, beta cell function can be associated with raised pro-insulin levels or otherwise.

Keywords: Type-2 diabetes mellitus (T2DM), Lipodystrophy, Pro-insulin, Adiponectin, Genome wide association studies (GWAS).

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Introduction

The term "Diabetes" was first used in literature by Araetus of Cappodocia around 100 AD.¹ The first technical classification appeared in 1979 by the "National Diabetes Data Group (NDDG)", which was further refined to expand multiple other categories including "gestational diabetes" and "other types" by American Diabetes Association (ADA) in 1997.² These definitions were still clinically utilized, till recent research highlighted certain discrepancies in type-2 diabetes mellitus (T2DM) management. Sakamoto M and others have acknowledged T2DM glycaemic and glycation variability

to drugs and differing complications rates among individuals.³⁻⁵ Hyperglycaemia associated with diabetes results in multiple complications including cardiovascular diseases and micro vascular diseases like nephropathy, neuropathies and retinopathy. However, it has been observed that rate of development of such complications is quite variable among people, races and ethnicities. After appreciating these phenotypic behaviours hidden between the currently defined "T2DM" phenotype, specific concerns with pharmacotherapy, regional and racial differences and long-term prognosis all joining hands to disallow quality healthcare for this epidemic disease.⁶ Time has really come to understand and identify the ultra-small differences for this heterogeneous disease to help decipher the differential pathophysiological categories, interpreting reasons for drug failures, predicting associated macro and micro complications. Moreover, data is replete with regional differences in terms of diabetes prevalence and complication rates, and well-conducted local studies clearly conclude genomic level differences between populations.⁷ Therefore bridging the old and gold phenotypic patterns with underlying genotypes will probably help us better appreciate the disease process with focused micro-precision patient related end outcome.

1- New molecular evidence

Since the earlier classification and introduction of molecular pathology tools in clinical and medical research, newer evidence has evolved which is going to change the landscape of this multi-dimensional medical disorder. Dupuis J et al have identified nine new genetic loci which can result in glycaemic variability among individuals with T2DM.⁸ Similarly, Wheeler E et al in a recent study has identified 60 genetic variants being common among T2DM subjects based upon their HbA1c levels.⁹ Genome wide association studies (GWAS) have allowed us a real mode of insight into these aforementioned variations tailed with T2DM.^{10,11} There is a definitive need for a more pragmatic approach to manage type-2 diabetes based upon recently highlighted phenotype-genotype linkages.

2- Suggested T2DM Classification

While rooted in genotype, the phenotypic differences can now be well-recognized, appropriately diagnosed,

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precisely managed and predicted for incoming complications. Literature search identifies multiple methods, general correlation and linkages between underlying gene polymorphisms and mutations which now replete Pubmed and other search engines, the overall simplicity provided by Udler MS et al which allowed a more realistic soft clustering methodology with genetic risk scores (GRS).¹¹ Therefore sub-classifying

T2DM is going to be a mandatory step in "micro-precision" era medicine for this emerging metabolic epidemic. Current evidence lacks complete comprehension, ever-evolving and changing with clinical needs which now demand more precise insights into molecular level defects. Issues associated with sub-classification of T2DM must be appreciated.

Generally 2 broader categories have been identified:

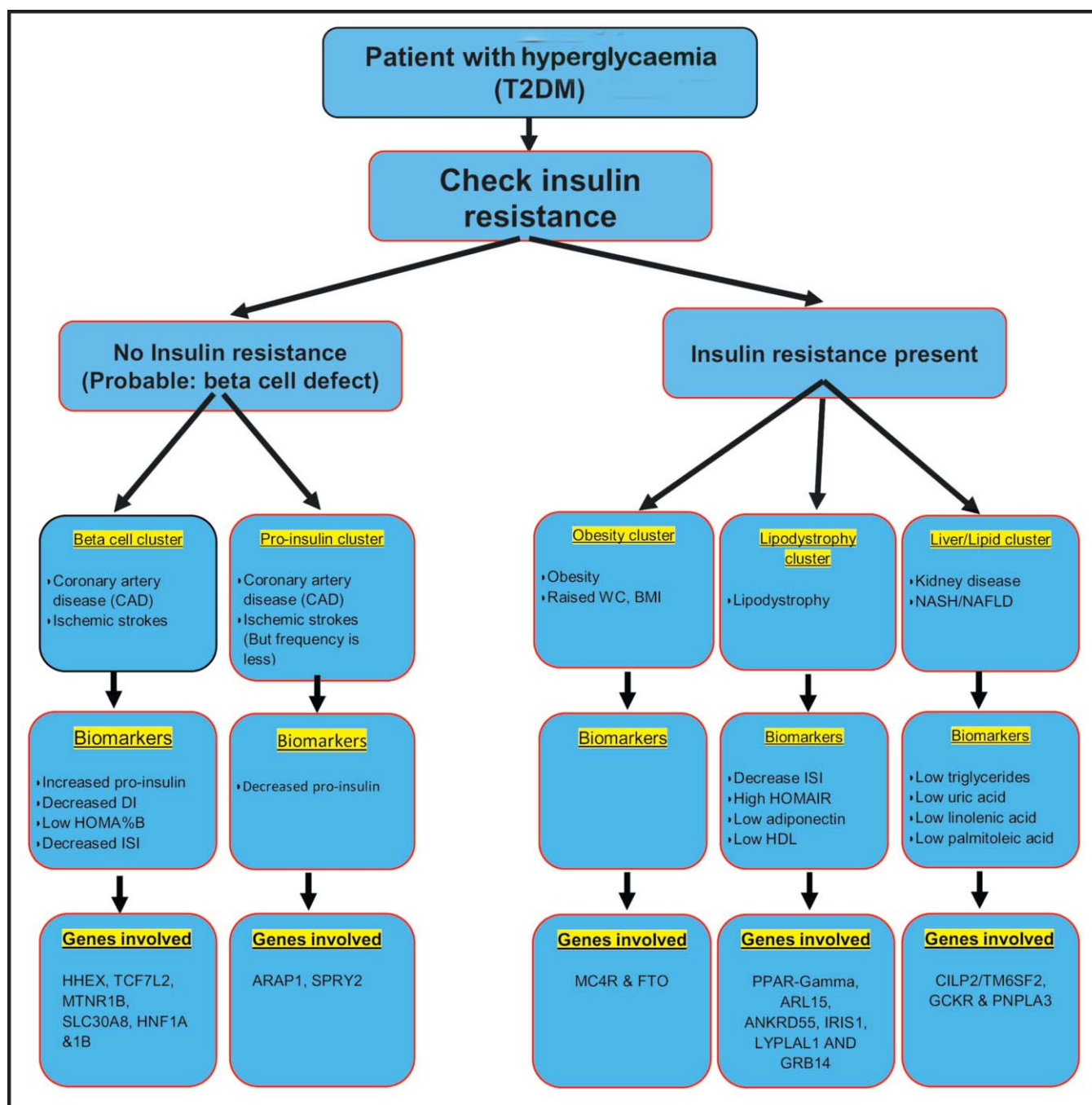


Figure-1: Suggested genotype-phenotype associating along with multiple sub-types within T2DM.

a. T2DM with beta cell dysfunction

This T2DM category deals with defects with beta cell dysfunction causing defective insulin production: There are two clusters within this domain:

1) Beta cell cluster: Primarily related with increased pro-insulin production, with further association in the form of decreased insulin release indices like Disposition Index (DI), insulin levels at 30-min post glucose load and HOMA-%B. The genetic loci associated with this cluster include HHEX, TCF7L2, MTNR1B, SLC30A8, HNF1A & 1B.¹²

2) Pro-insulin cluster: Main differentiating feature for this cluster is decreased pro-insulin. Here the main culprit genes include ARAP1, SPRY2.¹³

These clusters are more associated with higher frequency of coronary artery disease (CAD) and ischaemic stroke.¹¹

b. T2DM with Insulin resistance

1) Lipodystrophy cluster: This phenotype is associated with decrease insulin sensitivity index (ISI), increased HOMA-IR, low adiponectin and HDL-cholesterol along with fat-distribution like lipodystrophy.¹⁴ The genes associated with this type of cluster include: PPAR-Gamma, ARL15, ANKRD55, IRIS1, LYPLAL1 and GRB14.²⁰ Such T2DM variants have clinical spectra comprising hypertension with slightly higher association of CAD and ischaemic stroke.

2) Obesity cluster: Here the typical patient is obese with prominent genes involved include MC4R and FTO.¹⁵

3) Liver/lipid cluster: This T2DM pattern presents with low triglycerides, uric acid, linolenic acid and palmitoleic acid. Genes associated with this cluster include: CILP2/TM6SF2, GCKR and PNPLA3 which are sometimes also associated with NAFLD/NASH.¹⁶ Kidney disease is more prevalent with this variant.¹¹

Other molecular genotype-phenotype classifications are also available.¹⁷⁻¹⁹ However, each class address some different style and incorporate different genetic and biochemical biomarkers.

3- Suggested clinical approach

Using a combinatorial approach employing data from Udler MS et al,¹¹ Li L et al,¹⁷ Speliotes EK et al,¹⁶ Bonàs-Guarch S et al,¹⁴ Yaghootkar H et al¹⁵ and Chen P et al¹⁰ the term "T2DM" a methodology is suggested to appreciate genotype-phenotype model to appreciate the new data on the subject (Figure-1).

Discussion and Limitations

Our objective was to dissect the heterogeneity of the

broad spectrum disease labeled as "T2DM". If we could help understand and apply this phenotype-genotype information in our set up, treatment options can be wisely implemented. It must be acknowledged that the information shared above mostly based upon very recent but significant molecular data, which needs to be replicated across different races and further extended to incorporate pharmacogenomics information and disease prediction model. This desirable information will need specified randomized controlled trials and research pertinent to specific domains within T2DM category.

We understand limitations are there, and may be a few shortcomings due to rapidly evolving field of molecular medicine. It is hoped that the highlighted discussion will lead to quality research, systematic reviews and meta-analysis, and expert consensus guidelines. This may allow future clinicians with better diagnostic arsenals to match genotype-phenotype correlations, to provide therapeutic advice and to guide and predict patients regarding disease complications and prognosis.

Conclusion

This short communication was able to consolidate current genotype-phenotype correlation and highlighted the much needed awareness for clinicians to understand the critical differences existing between the broad-spectrum diseases labeled as "Type-2 diabetes mellitus". It is further expected that further authorities on diabetes to incorporate these medically relevant information into clinical guidelines to provide personalized management to patients and to individualize treatment related decisions.

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