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# Phenotyping Prediabetes

Prediabetes, defined by an HbA1c ranging from 5.7% to 6.4%, may be accompanied by an increased risk of complications before progression to overt diabetes type 2. This early pathophysiological dysregulation often remains undiagnosed. Recent studies are claiming different phenotypes of prediabetes.

One such study published in *Nature Medicine*[1] describes six pathophysiological phenotypic clusters using the oral glucose tolerance test (OGTT), fasting insulin, triglycerides (TRGs), HDL cholesterol, MRI-measured visceral and subcutaneous fat, liver fat assessed with H-MR spectroscopy, and a polygenic risk score for type 2 diabetes. Carotid intima thickness (IMT) was also measured together with pancreatic and renal hilar fat.

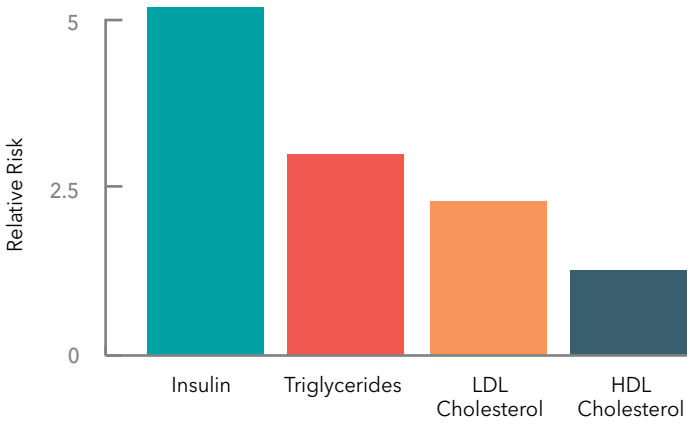


Figure 1

Cluster 1 was used as a control and was characterised by moderate diabetes progression risk accompanied by moderate insulin resistance and moderately abnormal TRGs and HDL levels.

Cluster 2 was characterised by low mortality together with a significantly lower risk of overt diabetes and coronary heart disease (CHD) than cluster 1. Insulin resistance was not a feature and TRGs and HDL were within normal limits.

Cluster 3 was characterised by high genetic risk (diabetes-associated G allele), the second highest progression to overt diabetes, pancreatic fat with disturbed insulin secretion, high carotid IMT but no increased CHD risk, however with a moderately elevated renal disease risk. Insulin resistance and TRGs were lower and HDL higher than in cluster 5.

Cluster 4 was characterised by predominantly subcutaneous fat ("healthy obesity") and low risk of progression to overt diabetes. This was accompanied by little insulin resistance, little liver fat, mild elevation of TRGs and mildly low levels of HDL.

Cluster 5 was associated with the highest progression to overt type 2 diabetes and all-cause mortality. It was characterised by high IMT, highest risk for kidney disease, highest insulin resistance, fatty liver, central obesity and the highest TRGs and lowest HDL levels.

Cluster 6 was characterised by high mortality in spite of low diabetes risk, most renal hilar fat and high risk for microalbuminuria and stage 3 renal disease, moderately high insulin resistance and TRGs level, moderately low HDL, high visceral fat and less liver fat.

At this stage of knowledge this study's clustering does not claim to be designed for definitive sub-phenotyping of patients. However, a few clinically useful conclusions may be drawn. In cluster 5 there is an imminent risk of established diabetes which should require intense diet and lifestyle intervention for weight loss and liver fat reduction. This applies also, albeit perhaps to a less intensive level, to cluster 3. In

cluster 6 insulin resistance, even with low glycaemia, appears to be responsible for renal disease and increased mortality. The pathogenesis of renal disease differs in type 1 and type 2 diabetes – glycaemia and hyperinsulinaemia respectively. This study also suggests fasting hyperinsulinaemia, TRGs and HDL levels are useful indicators of underlying early vascular pathology and the potential progression of prediabetes.

A recent study in *JAMA*[2] shows how the Mediterranean diet (mainly vegetables, legumes, fruit, nuts, seeds, olive oil, diary produce, fish and little red and preserved meat) lowers diabetes risk by 30% in overweight women. The most significant accompanying biomarker was a reduction of insulin resistance followed by HDL level improvement and BMI reduction, while LDL and HbA1c levels were irrelevant.

Fasting hyperinsulinaemia is an indication of chronically high insulin levels and insulin resistance. Chronic hyperinsulinaemia is associated with high blood pressure, increased platelet adhesiveness and atherosclerotic cardiovascular disease. Excess insulin (due to excess calorie consumption) accelerates ageing but not all calories stimulate insulin production to the same extent. Simple carbohydrates are the most powerful stimulators, protein to a much lesser extent, whereas fat has no effect on insulin.

The molecular basis of insulin resistance is unclear, but vascular endothelial dysfunction (a feature in type 2 diabetes) is the likely candidate, because insulin level in the interstitial space is lower than in the bloodstream. And endothelial dysfunction is the primary event in atherosclerosis.

A study published in *JAMA* in 1998[3] found that of the traditional risk factors for CHD, hyperinsulinaemia was more than twice as predictive as LDL (Figure 1). Also, TRGs were more predictive than LDL. One of the first signs of hyperinsulinaemia is increased TRGs. The fasting TRGs/HDL ratio is a surrogate marker for fasting insulin.

The pre-eminence of the predictive value of the TRGs/HDL for CHD risk was shown by a 1997 paper in *Circulation* (Figure 2).[4] Patients with the highest TRGs/HDL ratio were 16 times more likely to have a heart attack. High total cholesterol increased the risk by a factor of 2, while smoking increased the risk by a factor of 4.

Hyperinsulinaemia, and not fat (insulin neutral), would appear to be the main culprit in CHD. This crucial observation has been "hidden" from many cardiology departments by the huge LDL/statin industry (funding only statin/LDL trials). The finding that about 50% of patients hospitalised for CHD had total and LDL-cholesterol within normal limits[3] has also been overlooked. Statins probably improve CHD outcomes via their anti-inflammatory action on atherogenic lesions and not by lowering LDL.

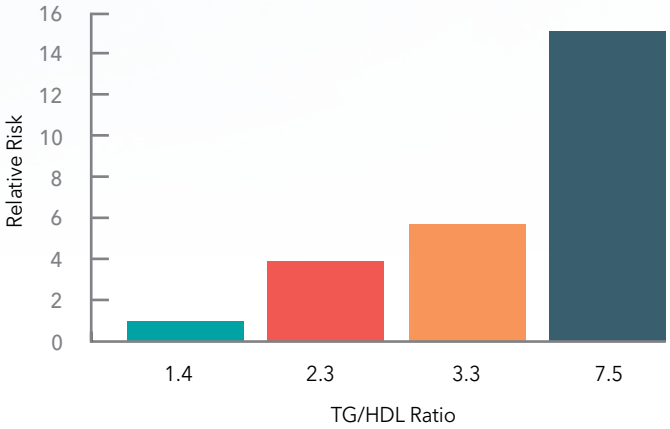


Figure 2

Reducing carbohydrate meal content (and alcohol) reduces insulin resistance, hyperinsulinaemia and the TRGs/HDL ratio. Marine omega-3 supplementation in adequate dosage (at least 3gm daily) also reduces TRGs.

Probably the most convenient method of assessing insulin production and diagnosing hyperinsulinaemia is measuring blood **C-peptide** level since this indicates how much insulin is being produced. Insulin and C-peptide are secreted into the portal vein in equimolar amounts but C-peptide's half-life is much longer than insulin's very short one and is therefore a more accurate measure of fasting/chronic insulin levels. Furthermore, the cumbersome OGTT test does not distinguish between insulin resistance and reduced insulin production. The C-peptide test seems simpler and superior to both blood insulin measurement and the OGTT. The C-peptide, HbA1c and TRGs/HDL ratio trio is suggested as a useful diagnostic and management tool in prediabetes and overt diabetes type 2.

To conclude, a very recent study[5] proposes another clinically useful prediabetes phenotypic cluster. In older adults (mean age 76 years), although prediabetes is common, the most common outcome is either return to normoglycaemia or death, and not progression to diabetes.

## REFERENCES


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