Pre-diabetes and the metabolic syndrome

V Gounden, MB ChB (Natal), FCP (Chem Path), MMed(Chem Path)

Consultant Pathologist, Department of Chemical Pathology, Inkosi Albert Luthuli Central Hospital, National Health Laboratory Service and University of KwaZulu-Natal, Durban

Correspondence to: V Gounden (verena.gounden@nhls.ac.za)

Definitions

The American Diabetes Association (ADA) defines pre-diabetes as a fasting plasma glucose (FPG) ≥5.6 mmol/l but <7.0 mmol/l, which is termed impaired fasting glycaemia (IFG), or an abnormal 2-hour response to a 75 g oral glucose tolerance test (OGTT) of at least 7.8 mmol/l and <11.1 mmol/l, which is termed impaired glucose tolerance (IGT), or an HbA_{1c} of 5.7 - 6.4%.[1] It is used to identify individuals with a greater risk of developing overt type 2 diabetes and also those at increased cardiovascular risk.[2] Pre-diabetes represents a continuum in the spectrum between normoglycaemia and overt hyperglycaemia.[2]

IFG/IGT is a characteristic feature of the metabolic syndrome (MetS).[3] The term MetS refers to a clustering of specific cardiovascular disease (CVD) risk factors.[3] The growing epidemic of obesity has fuelled the increase and interest in both pre-diabetes and MetS. The various criteria for MetS from different organisations are given in Table 1.

Laboratory investigations

Tests for insulin resistance

Insulin resistance is a feature common to both pre-diabetes and MetS and is regarded as being key in the pathogenesis of both conditions. No single laboratory test can be used to diagnose insulin resistance. Diagnosis is based on clinical findings corroborated with laboratory tests.[8]

- Impaired fasting glucose is characterised by fasting blood glucose values of ≥5.6 mmol/l and <7 mmol/l, based on a formal laboratory test glucose sample.[1]
- IGT – this is determined with the OGTT (also used in the diagnosis of diabetes mellitus). After an overnight fast patients are given a standard dose (75 g) of glucose in 200 ml of water; plasma glucose is measured before ingestion and 2 hours thereafter. OGTT is more sensitive and specific; however, it is less reproducible and more time consuming, expensive and inconvenient. In addition, prior daily carbohydrate intake must be at least 150 g for two weeks to obtain valid test results.

Table 1. Different criteria for the diagnosis of the metabolic syndrome

Clinical measure	NCEP ATP III[4]	IDF[5]	WHO[6]	Combined IDF, AHA/NHLBI (2009)[7] (3 out of 5 criteria)
Elevated waist circumference (WC)	WC >102 cm (men) WC >88 cm (women)	WC ≥94 cm for Europid men WC ≥80 cm for Europid women, with ethnicity-specific values for other groups	Waist:hip ratio > 0.9 in men and >0.85 in women BMI >30 kg/m^2	Population- and country-specific definitions
Elevated tiglycerides	≥1.7 mmol/l	≥1.7 mmol/l or on drug therapy for high triglycerides	≥1.7 mmol/l	≥1.7 mmol/l or on drug therapy for high triglycerides
Reduced HDL-C	<1 mmol/l in men < 1.3 mmol/l in women	<1.03 mmol/l in men <1.29 mmol/l in women, or specific treatment	<0.9 mmol/l in men <1.0 mmol/l in women	<1 mmol/l in men <1.3 mmol/l in women
Elevated blood pressure	Systolic ≥130 mmHg Diastolic ≥85 mmHg or on medication	Systolic ≥130/diastolic ≥85 mmHg/on antihypertensives	Systolic ≥140 mmHg Diastolic ≥90 mmHg/on medication	Systolic ≥130 mmHg Diastolic ≥85 mmHg
Elevated FPG Insulin resistance (IR)		FPG ≥5.6 mmol/l, or previously diagnosed type 2 diabetes	IR identified by one of the following: type 2 diabetes/IFG/IGT	≥5.6 mmol/l
Microalbumin	n/a	n/a	Urinary albumin excretion rate ≥20 µg /min Albumin:creatinine ratio ≥3.4 mg/mmol	n/a

- HbA_{1c} – global efforts to standardise the measuring and reporting of HbA_{1c} have seen this marker being included in the ADA criteria for the diagnosis of diabetes and the assessment of pre-diabetes.
- The gold standard for determining insulin resistance is the hyper-insulinaemic euglycaemic clamp study. Clamp studies specifically measure whole body insulin-mediated glucose uptake under controlled conditions of a combined glucose and insulin infusion.[9] However, these tests are too laborious for routine use and are rarely used in clinical practice. Various mathematical models have been used to determine formulas to act as surrogate markers of insulin resistance/sensitivity using fasting insulin and glucose measurements. One that is most often used is the homeostatic model assessment (HOMA) (Table 2).
- The measurement of insulin is hampered by the fact that it is an immunoassay and therefore the methods used and results generated may vary considerably from one laboratory to another (owing to a lack of assay standardisation).
- C-peptide – it ispart of the pro-insulin precursor molecule and released in equimolar amounts with insulin. C-peptide does not influence plasma glucose levels but is utilised as a marker of insulin production when measured in conjunction with glucose levels.[8]

Table 2. Some surrogate markers for determination of insulin resistance/sensitivity[8]

HOMA1-IR (insulin resistance) = (FPI* × FPG)/22.5
HOMA1-%B (B cell function) = (20 × FPI*)/(FPG – 3.5)
Quantitative insulin sensitivity check index (QUICKI) = 1/[log(FPI) + log(FPG)]
*FPI – fasting plasma insulin.

Dyslipidaemia

The lipid profile associated with MetS is raised fasting triglycerides and low concentrations of HDL cholesterol. Other lipoprotein abnormalities, e.g. increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles, and small HDL particles, have also been documented.[7] Although all of these have been implicated as being independently atherogenic, they do not form part of the diagnostic criteria for MetS and most are not routinely measured in laboratories.

Other

Microalbumin – the presence of urinary microalbumin is part of the WHO diagnostic criteria for MetS. It is measured using an early morning spot collection as a urine albumin:creatinine ratio or with a 24-hour urine collection and should be confirmed on at least two occasions. Microalbuminuria is a prognostic marker for CVD, a marker of incipient renal disease and a marker of inflammation.

C-reactive protein (CRP) – pre-diabetes and MetS are recognised as pro-inflammatory states. Obesity is related to increased production of pro-inflammatory cytokines and decreased production of the anti-inflammatory cytokine adiponectin by adipose tissue. Pro-inflammatory states are associated with increased cardiovascular risk and increased CRP levels. The measurement of high sensitivity CRP (hs CRP) has been recommended to assist in stratifying the risk for CVD.[7]

Uric acid – hyperuricaemia is commonly associated with MetS and has been postulated to play a causal role.

Diagnostic controversies

The criteria for pre-diabetes and MetS have evolved over the years and complete consensus regarding the definitions still has to be reached.

Overlap of IFG and IGT

There is controversy with regard to which test should be performed – fasting blood glucose (determining IFG) or OGTT (determining IGT). However, since the OGTT is a challenge test, it is likely that the detection rate will be higher. Generally, among subjects screened using IGT, only 20 - 25% have FPG levels that would indicate impaired fasting glucose. In subjects screened with IFG, <50% have a postprandial 2-hour glucose level of ≥7.8 mmol/l.[2] Also, the diagnosis of subjects screened using the HbA_{1c} criterion has been shown to not be completely consistent with IFG and IGT methods for the diagnosis/screening of pre-diabetes.[9]

References available at www.cmej.org.za

Vitamin D in clinical practice

A E Zemlin, MB ChB, MMed (Chem Path), FC Path (SA) Chem
Senior Specialist/Senior Lecturer, Department of Chemical Pathology, Stellenbosch University and National Health Laboratory Service, Tygerberg Hospital and Green Point Laboratories

C Meyer, MB ChB, MMed (Chem Path)
Senior Specialist/Senior Lecturer, Department of Chemical Pathology, Stellenbosch University and National Health Laboratory Service, Tygerberg Hospital and Green Point Laboratories

Correspondence to: A Zemlin (azemlin@sun.ac.za)

Background

Vitamin D was first described in the 20th century when a cause for the high prevalence

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