



International Diabetes Federation
Avenue Emile De Mot 19
B-1000 Brussels, Belgium
Telephone +32-2-5385511
Telefax +32-2-5385114
info@idf.org
www.idf.org | VAT BE433.674.528

Embargo: Thurs 14th April 2005 at 12:30 (CET)

The IDF consensus worldwide definition of the metabolic syndrome

Part 1: Worldwide definition for use in clinical practice

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (*defined as waist circumference \geq 94cm for European men and \geq 80cm for European women, with ethnicity specific values for other groups*)

plus any two of the following four factors:

- **raised TG level:** $>$ 150 mg/dL (1.7 mmol/L), **or specific treatment for this lipid abnormality**
- **reduced HDL cholesterol:** $<$ 40 mg/dL (0.9 mmol/L) in males and $<$ 50 mg/dL (1.1 mmol/L) in females, **or specific treatment for this lipid abnormality**
- **raised blood pressure:** systolic BP \geq 130 or diastolic BP \geq 85 mm Hg, **or treatment of previously diagnosed hypertension**
- **raised fasting plasma glucose (FPG) \geq 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes**
If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, **central obesity** and **insulin resistance** are acknowledged as important causative factors.¹⁻⁵

Central (abdominal) obesity, easily assessed using waist circumference and independently associated with each of the other metabolic syndrome components including insulin resistance,^{2,6} is a prerequisite risk factor for the diagnosis of the syndrome in the new definition. Insulin resistance, which is difficult to measure in day-to-day clinical practice, is not an essential requirement.

Atherogenic dyslipidaemia describes the combination of raised triglycerides (TG) and low concentrations of HDL-c together with elevated apolipoprotein B (ApoB), small dense LDL and small HDL particles, all of which are independently atherogenic,⁷ and which is commonly observed in patients with both type 2 diabetes and the metabolic syndrome. Low HDL-c and high TG levels are frequently found with insulin resistance, with or without type 2 diabetes,⁸ and both are risk factors for coronary heart disease (CHD).^{9,10}



Table 2: Ethnic specific values for waist circumference

Central obesity is most easily measured by waist circumference using the guidelines in Table 2 which are gender and ethnic-group (not country of residence) specific. The consensus group acknowledges that these are pragmatic cut-points taken from various different data sources and that better data will be needed to link these to risk.

Country/Ethnic group		Waist circumference*
Europids <i>In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes</i>	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians <i>Based on a Chinese, Malay and Asian-Indian population</i>	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese	Male	≥ 85 cm
	Female	≥ 90 cm
Ethnic South and Central Americans	<i>Use South Asian recommendations until more specific data are available</i>	
Sub-Saharan Africans	<i>Use European data until more specific data are available</i>	
Eastern Mediterranean and Middle East (Arab) populations	<i>Use European data until more specific data are available</i>	

* *In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.*

Although a higher cut-point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that for epidemiological studies and, wherever possible, for case detection, ethnic group specific cut-points should be used for people of the same ethnic group wherever they are found. Thus the criteria recommended for Japan would also be used in expatriate Japanese communities, as would those for South Asian males and females regardless of place and country of residence.¹¹



Part 2: 'Platinum standard' definition—additional metabolic criteria for research

The IDF consensus group has highlighted a number of other parameters that appear to be related to the metabolic syndrome (Table 3) which should be included in research studies to help determine the predictive power of these extra criteria for CVD and/or diabetes. The use of these additional factors in research will also allow further modification of the definition if necessary and the validation of the new clinical definition in different ethnic groups.

Table 3: Additional metabolic criteria for research

Abnormal body fat distribution	General body fat distribution (DXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidaemia (beyond elevated triglyceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycaemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein (SAA) Elevated inflammatory cytokines (eg TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1 etc) Clotting factors (fibrinogen etc)
Hormonal factors	Pituitary-adrenal axis



Part 3: Recommendations for treatment

Once a diagnosis of the metabolic syndrome is made, the future management of the condition should be aggressive and uncompromising in its aim to reduce the risk of CVD and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment (including smoking status) in conjunction with the following:

- **Primary intervention**

IDF recommends that primary management for the metabolic syndrome is healthy lifestyle promotion. This includes:

- moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
- moderate increase in physical activity
- change in dietary composition

The results of Finnish and American prevention of diabetes studies have shown the marked clinical benefits associated with a small weight loss in terms of preventing (or at least delaying by several years) the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese.^{12,13}

- **Secondary intervention**

In people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, drug therapy may be required to treat the metabolic syndrome. While there is a definite need for a treatment that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long term metabolic and cardiovascular consequences, these mechanisms are currently unknown and specific pharmacological agents are therefore not yet available. As defined in Table 4, it is currently necessary instead to treat the individual components of the syndrome in order that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk.

Table 4: IDF recommended treatment of the individual components of the metabolic syndrome

Atherogenic dyslipidaemia
<p>Primary aims for therapy:</p> <ul style="list-style-type: none">• Lower TG (as well as lowering ApoB and non-HDL cholesterol)• Raise HDL-c levels• Reduce LDL-c levels (elevated levels represent a high risk in the metabolic syndrome) <p>Options:</p> <ul style="list-style-type: none">• Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD in people with metabolic syndrome. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-c concentrations using a fibrate in patients with well-established CHD and both a low HDL-c and a low LDL-c level will significantly reduce the incidence of major coronary events.⁸• Statins to reduce all ApoB-containing lipoproteins and to achieve ATP III goals for LDL-c as well as for non-HDL-c (ATP III, 2001). Several clinical studies have confirmed the benefits of statin therapy.^{14–16}



- Fibrates in combination with statins but may be complicated by side effects

Elevated blood pressure

- Categorical hypertension (BP $\geq 140/\geq 90$ mm Hg) should be treated according to the USA Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) recommendations.¹⁷
- In patients with established diabetes, antihypertensive therapy should be introduced at BP $\geq 130/\geq 80$ mm Hg.

Options:

- Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, with some clinical trials (but not all) suggesting they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials suggest that the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug.
- No particular agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

Insulin resistance and hyperglycaemia

There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk when metabolic syndrome is present. The Diabetes Prevention Program (DPP) showed that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes and recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing type 2 diabetes in patients with impaired glucose tolerance (IGT) and insulin resistance.^{18,19,20} Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in patients with IGT.^{21,22}

Data do not yet exist to show whether any of the currently available thiazolidinediones reduce the risk of CVD in those with the metabolic syndrome, IGT or diabetes.

The group awaits with interest the results of ongoing thiazolidinedione and fibrate outcomes studies, as well as the publication of clinical data for the new generation of PPAR agonists which interact with both PPAR alpha and gamma receptors, thereby combining lipid and glycaemic effects. In addition, emerging therapies such as incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, and the endocannabinoid receptor blocking agents offer potential as future therapies for the metabolic syndrome.



Part 4: Future work

The IDF consensus group hopes that this new definition, emphasising the importance of central obesity with modifications according to ethnic group, will be adopted worldwide and prove convenient and useful in clinical practice and epidemiological studies. This should encourage the clinical diagnosis of the metabolic syndrome and the identification of patients at considerably increased risk of developing CVD and/or type 2 diabetes. A single worldwide definition will enable easier comparison of data from different studies and the ongoing refinement of the definition as more information becomes available and as the following areas of further research are explored:

- the aetiology of the metabolic syndrome
- the best and most predictive definition of the metabolic syndrome and its components
- how blood pressure is related to the other components of the syndrome
- the relationship between different constellations of factors to CVD outcomes
- the relationship of simple and complex measures of the components of the metabolic syndrome to clinical events
- the true impact of effective treatment of all components of the syndrome on CVD risk
- better identification of high risk patients with metabolic syndrome in different populations

References

1. Anderson PJ, Critchley JAJH, Chan JCN et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. *International Journal of Obesity* 2001;**25**:1782
2. Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes* 2004;**53(8)**:2087-94
3. Nakamura T, Tokunga K, Shimomura I et al. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994;**107**:239-46
4. Bonora E, Kiechl S, Willeit J et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 1998;**47(10)**:1643-9
5. Nesto RW. The relation of insulin resistance syndromes to risk of cardiovascular disease. *Rev Cardiovasc Med* 2003;**4(6)**:S11-S18
6. Pouliot MC, Després JP, Lemieux S et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;**73**:460-8
7. Brunzell JD, Ayyobi AF. Dyslipidemia in the metabolic syndrome and type 2 diabetes mellitus. *Am J Med* 2003 Dec 8;**115 Suppl 8A**:24S-28S
8. Robins SJ, Rubins HB, Faas FH et al. Insulin resistance and cardiovascular events with low HDL cholesterol. The Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care* 2003;**26(5)**:1513-7



9. Steinmetz A, Fenselau S, Schrezenmeir J. Treatment of dyslipoproteinemia in the metabolic syndrome. *Exp Clin Endocrinol Diabetes* 2001;**109**:S548-59
10. Robins SJ, Collins D, Wittes JT et al. Relation of Gemfibrozil treatment and lipid levels with major coronary events. *JAMA* 2001;**285**:1585-91
11. Tan CE, Ma S, Wai D et al. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004;**27**:1182-6
12. Lindström J, Louheranta A, Mannelin M. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 2003;**26**:3230-6.
13. Tuomilehto J, Lindström J, Eriksson JG et al. Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *NEJM* 2001;**344**:1343-50
14. Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**:2005-16
15. Haffner SM, Alexander CM, Cook TJ et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes mellitus or impaired fasting glucose levels: subgroup analysis on the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;**159**(22):2661-7
16. Goldberg RB, Mellies MJ, Sacks FM et al. for the CARE investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998;**98**:2513-9.
17. Chobanian AV, Bakris GL, Black HR et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;**42**(6):1206-52
18. Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM* 2002;**346**(6):393-403
19. Buchanan TA, Xiang AH, Peters RK et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002;**51**:2796-803
20. Durbin RJ. Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. *Diabetes, Obesity and Metabolism* 2004;**6**:280-5
21. Chiasson JL, Josse RG, Gomis R et al. STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003 Jul 23;**290**(4):486-94.
22. Torgerson JS, Hauptman J, Boldrin MN et al. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;**27**:155-61.