

Original Article:

Assessment of the risk for metabolic syndrome in prediabetes and newly-diagnosed type 2 diabetes* T.I. Tankova¹, N.Y. Chakarova¹, L.N. Dakovska¹, K.B. Kalinov², I.A. Atanassova¹**Abstract:**

The aim of the present study was to assess the risk for metabolic syndrome (MetS) in subjects with prediabetes - impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) and in newly-diagnosed type 2 diabetes (NDD). The metabolic syndrome parameters (according to 2005 IDF definition) and high-sensitive C-reactive protein (hsCRP) were measured in 727 subjects - 238 with IFG, 184 with IGT and 305 with NDD. The unadjusted prevalence of MetS was 84.03% in IFG, 89.13% in IGT and 89.51% in NDD. The odds ratio (OR) for prevalent MetS was 8.82 (95% CI, 3.19-19.8, $p < 0.001$) in IFG, 11.26 (95% CI, 4.18-24.6, $p < 0.001$) in IGT and 4.87 (95% CI, 2.10-9.50, $p < 0.001$) in NDD. Of the different studied parameters, the OR for metabolic syndrome was significant for female sex - 2.31 (95% CI, 1.45-4.35, $p = 0.009$), fasting plasma glucose - 2.30 (95% CI, 1.56-3.40, $p < 0.001$), waist circumference - 1.36 (95% CI, 1.12-1.42, $p < 0.001$), HDL-cholesterol - 0.273 (95% CI, 0.14-0.52, $p = 0.01$) and triglycerides - 3.84 (95% CI, 2.61-5.66, $p < 0.0001$). Significantly higher hsCRP levels were found in all groups with MetS as compared to those without MetS. The prevalence of MetS in pre-diabetes is rather high, being similar to that in newly-diagnosed type 2 diabetes. The risk for MetS is even higher in pre-diabetes as compared to NDD. Therefore IFG and IGT should be considered not just as conditions of altered glucose metabolism but also in relation to their association with cardiovascular risk factors.

Key words: Metabolic Syndrome, Prediabetes, IFG, IGT, type 2 diabetes**Introduction:**

Metabolic syndrome (MetS) represents an aggregation of metabolically related cardiovascular risk factors including obesity, raised blood pressure, impaired glucose tolerance and dyslipidemia. Since its initial description, several expert groups have produced different definitions [1-3], the most recent one being proposed by the International Diabetes Federation (IDF) in 2005, recognizing that visceral fat accumulation is essential in the development of the syndrome [4].

Hypothesis relating central adiposity to the MetS focus on the newly emerging understanding that

visceral adipose tissue is considered an endocrine organ of high activity, producing a number of molecules, cumulatively named as adipokines [5,6] that play a role in energy homeostasis, carbohydrate and energy metabolism, and impaired insulin action, leading to insulin resistance.

What is very clear from current epidemiological data is that the MetS is a frequent and increasing problem everywhere in the world, affecting around a quarter of the world's adult population [7]. The high prevalence of MetS has important health implications. It is considered to be a driver of the modern day epidemics of diabetes and cardiovascular diseases (CVD) [8,9]. A number of studies have confirmed that the risks of developing CVD, and of both cardiovascular and all-causes of mortality, are increased by the presence of MetS [10-13].

The risk for diabetes is up to fivefold higher in patients with metabolic syndrome [14]. Most patients who develop type 2 diabetes mellitus are obese, predominantly with abdominal obesity. Thus diabetes and metabolic syndrome quite frequently coexist [15]. The term "prediabetes" is cumulative for two intermediate conditions - impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [16]. In fact, the

¹Department of Diabetology, Clinical Centre of Endocrinology, Medical University, Sofia, Bulgaria

² New Bulgarian University, Sofia, Bulgaria

Corresponding Author:*Dr. Tsvetalina Tankova MD, PhD**

Associate Professor

Clinical Centre of Endocrinology

University Hospital of Endocrinology

Medical University, Sofia

12, Narodno Sabranie sq.

1000 - Sofia, Bulgaria

E mail: tankova@iname.com

glucose intolerance in the metabolic syndrome could be IFG, IGT or diabetes. In clinical practice, the presence of any one of these glucose abnormalities will suffice; still glucose intolerance being just one of the components of MetS and not an obligatory one.

The aim of the present study was to assess the risk for metabolic syndrome in subjects with pre-diabetes - IFG and IGT, and in newly-diagnosed type 2 diabetic patients.

Methodology:

A total of 727 subjects were included in the study - 238 with IFG (88 males and 150 females), mean age 52.1 ± 11.4 years; 184 with IGT (62 males and 122 females), mean age 55.1 ± 14.1 years; and 305 with newly-diagnosed diabetes - NDD (138 males and 167 females), mean age 56.6 ± 12.2 years. They were selected among participants in a screening program for people at risk of developing type 2 diabetes (having at least one of the main risk factors for diabetes - a first degree relative with type 2 diabetes; overweight or central obesity; history of gestational diabetes; delivery of a baby over 4 kg; history of IFG or IGT, arterial hypertension; lipid abnormalities; clinically established atherosclerotic vascular disease) at the Department of Diabetology, University Hospital of Endocrinology, Medical University, Sofia during the period from April 2006 - December 2009. The participants were recruited by referrals by specialists and general practitioners as well as after advertisement in local media. All subjects declared their written informed consent for participation after full explanation of the aims and design of the study. The study was approved by the Ethics Committee of the Medical University, Sofia and all the procedures followed were in accordance with the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

All participants underwent a standard oral glucose tolerance test (OGTT) with 75g glucose and the categories of glucose tolerance were defined according to 2006 WHO criteria [15]. Plasma glucose during OGTT - fasting and 2-hour level, was measured by a hexokinase enzyme method. Serum lipid parameters (total cholesterol, HDL cholesterol, triglycerides) were assessed using enzyme-colorimetric tests; LDL cholesterol was calculated using Friedwald's formula. High-sensitive C-reactive protein (hsCRP) was measured by a turbidimetric

method. Anthropometric methods were applied - measurement of height, weight, waist circumference (measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest). Arterial blood pressure was measured in standard conditions 3 times, after a 5-minute rest. The 2005 IDF definition of the metabolic syndrome was used [4].

Statistical analysis of the data was performed by SPSS 16.0 for Windows (SPSS, Chicago, USA). The data is expressed as means \pm standard deviation (SD). Student's t-test and one-way analysis of variance (ANOVA) were used to compare continuous variables. Comparisons were accomplished between subjects with IFG, IGT and newly-diagnosed diabetes with and without metabolic syndrome. Bonferroni's correction for multiple comparisons was applied where appropriate. Logistic regression was applied to estimate the odds ratios (OR) and corresponding 95% confidence intervals [CI] for the different explanatory variables used to predict metabolic syndrome. In addition, the same model was used for assessing odds ratio for metabolic syndrome within the different groups - with IFG, IGT and newly-diagnosed diabetes. Hosmer-Lemeshow chi-square statistic was used as for goodness-of-fit criteria. A significance level of 0.05 was considered as proper, and thus p-values (two tailed) of less than 0.05 were considered statistically significant.

Results

Based on the IDF definition, the unadjusted prevalence of the metabolic syndrome was 84.03% in IFG subjects, 89.13% in IGT subjects and 89.51% in newly-diagnosed diabetic patients. Metabolic syndrome was present in 76.1% of males and in 88.6% of females with IFG; in 83.9% of males and in 91.8% of females with IGT; and in 83.3% of males and in 94.0% of females with newly-diagnosed diabetes. Thus in males the metabolic syndrome was equally prevalent in IGT and NDD groups and least prevalent in IFG group, while in females it was most prevalent in newly-diagnosed diabetes.

The anthropometric parameters (BMI, waist circumference in males and females) of the subjects with IFG, IGT and newly-diagnosed diabetes with and without the metabolic syndrome are presented in Table 1.

Table 1. Anthropometric parameters – body mass index (BMI) and waist circumference in males and females in the groups with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and newly-diagnosed diabetes (NDD) with (MetS+) and without (MetS-) the metabolic syndrome.

	IFG		IGT		NDD	
	MetS+ (n=200)	MetS- (n=38)	MetS+ (n=164)	MetS- (n=20)	MetS+ (n=273)	MetS- (n=32)
BMI (kg/m²)	32.4±6.3	25.7±4.2	30.9±5.3	24.6±3.9	31.8±6.1	25.3±3.5
Waist circumference (cm) males	107.0±10.1* (n=67)	93.3±11.2 (n=21)	112.7±12.5 (n=52)	87.5±6.5 (n=10)	112.2±14.9 (n=116)	91.6±7.0 (n=22)
Waist circumference (cm) females	106.1±13.3# (n=133)	90.4±14.5 (n=17)	101.9±11.4* (n=112)	92.4±13.3 (n=10)	105.6±12.3 (n=157)	89.9±15.6 (n=10)

* p<0.01 vs NDD with MetS # p<0.01 vs IGT with MetS

Table 2. Lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) and hsCRP levels in the groups with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and newly-diagnosed diabetes (NDD) with (MetS+) and without (MetS-) the metabolic syndrome.

	IFG			IGT			NDD		
	MetS+ (n=200)	MetS- (n=38)	p ^a	MetS+ (n=164)	MetS- (n=20)	p ^a	MetS+ (n=273)	MetS- (n=32)	p ^a
Total cholesterol	5.85±1.1	5.45±1.11	=0.04	5.77±1.2	4.98±1.19	=0.006	5.86±1.17	5.67±1.2	>0.1
HDL cholesterol	1.27±0.36***	1.51±0.4	=0.0003	1.2±0.34	1.4±0.35	=0.01	1.15±0.33	1.45±0.37	<0.0001
LDL cholesterol	3.78±1.0	3.47±1.0	>0.1	3.63±1.04	3.44±1.0	>0.1	3.69±1.04	3.62±0.96	>0.1
Triglycerides	1.77±1.0**** #	1.04±0.39	<0.0001	2.19±1.3	0.98±0.37	<0.0001	2.3±1.63	1.31±0.78	<0.0001
hsCRP	4.98±3.25*	2.34±1.83	<0.0001	4.44±3.06**	2.99±3.3	=0.04	5.75±4.79	3.19±2.38	<0.001

p^a – between the corresponding groups with and without MetS

* p<0.05 vs NDD with MetS; ** p<0.01 vs NDD with MetS; *** p<0.001 vs NDD with MetS; **** p<0.0001 vs NDD with MetS

p<0.001 vs IGT with MetS

BMI was similar in the three groups with metabolic syndrome – 32.4 ± 6.3 kg/m² in IFG, 30.9 ± 5.3 kg/m² in IGT and 31.8 ± 6.1 kg/m² in NDD. Waist circumference was similar in males with IGT and NDD and MetS, being significantly higher in both groups as compared to IFG. In females, waist circumference was similar in IFG and NDD, being significantly higher in both groups as compared to IGT with MetS.

The levels of the lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) and hsCRP of the different groups.

IFG, IGT and screening-detected diabetes with and without the metabolic syndrome are presented on Table 2.

Of the different studied parameters, the OR for prevalent metabolic syndrome was significant for female sex – 2.31 (95% CI, 1.45-4.35, $p=0.009$), fasting plasma glucose – 2.30 (95% CI, 1.56-3.40, $p<0.001$), waist circumference – 1.36 (95% CI, 1.12-1.42, $p<0.001$), HDL-cholesterol – 0.273 (95% CI, 0.14-0.52, $p=0.01$) and triglycerides – 3.84 (95% CI, 2.61-5.66, $p<0.0001$). (Table 3)

Table 3. Odds ratio (OR) for prevalent metabolic syndrome for the different anthropometric and laboratory parameters in all studied subjects.

Variables	Odds ratio (OR)	95.0% C.I.		p
		Lower	Upper	
Sex (female)	2.313	1.450	4.349	0.009
Fasting plasma glucose	2.30	1.56	3.40	<0.001
Plasma glucose (120 min)	1.060	0.926	1.212	0.4
HbA1c	1.055	0.751	1.482	0.7
Total cholesterol	0.762	0.512	1.135	0.13
HDL-cholesterol	0.273	0.143	0.521	0.01
LDL-cholesterol	0.816	0.743	0.956	0.34
Triglycerides	3.84	2.611	5.661	0.0001
Arterial hypertension	0.996	0.959	1.035	0.83
hsCRP	0.991	0.933	1.051	0.75
BMI	1.028	0.942	1.123	0.53
Waist circumference	1.36	1.12	1.42	0.014
Systolic blood pressure	1.008	0.992	1.044	0.29
Diastolic blood pressure	1.028	0.899	1.048	0.32

The OR for prevalent metabolic syndrome was 8.82 (95% CI, 3.19-19.8, $p<0.001$) in IFG group, 11.26 (95% CI, 4.18-24.6, $p<0.001$) in IGT group and 4.87 (95% CI, 2.10-9.50, $p<0.001$) in the group with newly-diagnosed diabetes. Our results demonstrated certain differences in the OR for prevalent metabolic syndrome in males and females – the OR for metabolic syndrome in females was 12.83 (95% CI, 4.5-27.1, $p<0.001$) in

IFG group, 8.02 (95% CI, 3.73-16.31, $p<0.001$) in IGT group and 6.89 (95% CI, 2.73-10.31, $p<0.001$) in the group with newly-diagnosed diabetes; in males the OR was 5.94 (95% CI, 2.36-13.46, $p<0.001$) in IFG group, 10.59 (95% CI, 3.94-27.85, $p<0.001$) in IGT group and 2.6 (95% CI, 1.33-5.32, $p<0.001$) in the group with newly-diagnosed diabetes, respectively.

Discussion

The metabolic syndrome, diabetes and prediabetes have become major public health problems in recent decades, and are increasing in prevalence around the world [17]. Still the glucose dysregulation present in the syndrome is just one of the factors and not an obligatory one [1-4].

Our results demonstrate a rather high prevalence of MetS in both IFG and IGT and in screening-detected type 2 diabetes – 84.03%, 89.13% and 89.18%, respectively. It should be pointed out that the estimated prevalence might be influenced to some extent by the inclusion criteria used as some of them are components of the MetS – e.g. hypertension, lipid abnormalities, overweight or central obesity. Nevertheless, the aim of the study was to assess the risk of MetS in different categories of glucose intolerance. The rationale for identifying subjects with glucose abnormalities (prediabetes and NDD) is performing a targeted screening among individuals having one or more risk factors for developing diabetes some of which are also the criteria for defining the presence of MetS. Thus it appears that not just diabetes but prediabetes and metabolic syndrome also quite frequently coexist. Considering the OR for metabolic syndrome in the different groups – IFG, IGT and newly-diagnosed diabetes, prediabetes appears to be an even stronger predictor for metabolic syndrome as compared to diabetes. Our results demonstrate some gender differences in the risk for prevalent metabolic syndrome – the OR was found to be significantly higher in females – 2.31 (95% CI, 1.45-4.35, $p=0.009$). Furthermore, in females the highest OR for prevalent metabolic syndrome was established in the group with IFG, while in males the highest OR appeared to be in the group with IGT.

We have used the latest definition of the metabolic syndrome (IDF, 2005) [4]. In fact all expert groups agree on the core components of the MetS – visceral obesity, glucose intolerance, dyslipidaemia and arterial hypertension [1-4]. However, they provide different clinical criteria to identify such a cluster. The IDF considers the obesity epidemic to be one of the main drivers of the high prevalence of the MetS. With the development of imaging techniques to measure central fat precisely, several studies have shown that central fat accumulation is predictive of the features of the MetS [18,19,20,21]. Furthermore, it

has now been documented that individuals with a normal BMI may nevertheless be characterized by an excess of visceral adipose tissue and show the features of the MetS. The use of waist circumference to assess abdominal adiposity appears to be superior to BMI [19]. This is well-documented in our study, demonstrating stronger correlation between waist circumference and MetS ($r=0.69$, $p<0.001$) as compared to that between BMI and MetS ($r=0.41$, $p<0.01$) in all studied subjects – with IFG, IGT and newly-diagnosed diabetes. The OR for prevalent MetS was significant for waist circumference, but not significant for BMI.

The high prevalence of MetS observed in diabetes and prediabetes could be partly due to the definition used because several studies have reported higher prevalence when using 2005 IDF definition as compared to WHO, EGIR and ATP III criteria [7].

Our results demonstrate significantly higher triglyceride levels and significantly lower HDL cholesterol levels between the subjects with MetS and without MetS in all studied groups – with IFG, IGT and NDD. This represents the typical lipid profile associated with the metabolic syndrome, characterized by increased plasma triglyceride level, as well as reduced HDL cholesterol and an increased proportion of small, dense, cholesteryl ester – depleted LDL particles with relatively normal or only mildly elevated LDL cholesterol concentration [22,23]. LDL cholesterol levels appeared to be similar in all three groups – IFG, IGT and NDD both with MetS and without MetS. A more precise analysis of the proatherogenic changes in serum lipids would have been performed if LDL particle size was measured as qualitative rather than quantitative changes in LDL cholesterol are typical for the atherogenic dyslipidemia in the metabolic syndrome. Insulin resistant visceral adipocytes are more sensitive to the lipolytic effects of glucocorticoids and catecholamines, which increase the release of free fatty acids into the portal system, promoting hepatic synthesis of triglycerides and VLDL. Our results demonstrate similar lipid profiles in the subjects with IGT and NDD with MetS. The group with IFG and MetS presented with significantly higher levels of HDL cholesterol as compared to NDD ($p<0.001$) and significantly lower levels of triglycerides as compared to NDD ($p<0.0001$) and IGT ($p<0.001$) with MetS. Amongst all studied parameters the risk (OR) for metabolic syndrome was highest for triglycerides – 3.84 (95% CI, 2.61-

5.66, $p < 0.0001$). (Table 3) The presence of arterial hypertension and the level of systolic and diastolic blood pressure appeared not to be of significant importance for the overall risk for MetS in the studied setting.

A proinflammatory state is recognized by elevated C-reactive protein (CRP) levels and is commonly present in subjects with the MetS [24]. Our results demonstrate significantly higher hsCRP levels in all studied groups – IFG, IGT and screening-detected diabetes with MetS as compared to those without MetS. The values of hsCRP are found to be similar in the two prediabetic groups with MetS, both being significantly lower as compared to those of the diabetic patients with MetS. Thus a proinflammatory state is present in both prediabetes and type 2 diabetes. A significant relationship has been reported between plasma CRP levels and measures of adiposity and of insulin resistance [25-27]. Data from the USA have shown that the risk of having an elevated CRP rises in a graded manner with increasing the number of components of the MetS [28]. One contributory mechanism to this association is visceral obesity, as adipocytes and macrophages release inflammatory cytokines which promote an inflammatory state [24]. Thus the presence of MetS appears to be associated with higher CRP levels in all studied groups with different glucose intolerance.

Although there is agreement that the metabolic syndrome is a major public health challenge worldwide and consistent evidence stresses the need for intervention, still some studies have disputed whether the MetS gives any additional information over and above the individual well-known CVD risk factors [29]. Still some international organizations, including the American Diabetes Association (ADA), question the value of the specific diagnosis of metabolic syndrome. They point out that the criteria, taken together, are no more useful at predicting the risk of cardiovascular disease or diabetes than the individual criteria considered separately. The metabolic syndrome has been reported to be a marker of CVD risk, but not above and beyond the risk associated with its individual components [30].

The established high prevalence of MetS is not unexpected in newly-diagnosed type 2 diabetic patients, keeping in mind that over 80 % of them are overweight or obese. But it is really surprising

to have nearly the same prevalence of the metabolic syndrome in subjects with prediabetes – IFG and IGT. The two prediabetic conditions are considered different as far as their association with cardiovascular risk is concerned, IGT being more strongly related to the CVD outcomes. [31,32]. Still according to the results of this study the two prediabetic states appear to be rather similar in relation to the prevalence of the MetS, and therefore in relation to cardiovascular risk. In fact the level of fasting plasma glucose and not that of postprandial glucose appeared to be associated with a significant risk (OR) for prevalent metabolic syndrome – 2.30 (95% CI, 1.56-3.40, $p < 0.001$).

Conclusion

The prevalence of the metabolic syndrome in prediabetes – IFG and IGT, is rather high, being similar to that in newly-diagnosed type 2 diabetes. The risk for metabolic syndrome is even higher in prediabetes as compared to newly-diagnosed diabetes. Therefore IFG and IGT should be considered not just as conditions of altered glucose metabolism but also in relation to their association with cardiovascular risk factors.

Acknowledgement

This study was supported by a grant (308/2007) of the Ministry of Education and Science, Bulgaria.

References

1. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Geneva: World Health Organization 1999.
2. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999, 16:442-443.
3. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001, 285:2486-2497.
4. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006, 23:469-480.

5. Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes Relat Metab Disord* 2004, 28:1018-1025.
6. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. *Am J Med Sci* 2005, 330:280-289.
7. Ford FS. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005, 28:2745-2749.
8. Haffner SM, Cassells HB. Metabolic syndrome – a new risk factor of coronary heart disease. *Diab Obes Metab* 2003, 5:359-370.
9. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001, 24:683-689.
10. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 2004, 164:1066-1076.
11. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP; San Antonio Heart Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation* 2004, 110:1251–1257.
12. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002, 288:2709-2716.
13. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 2005, 28:385-390.
14. Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 2004, 27:2676-2681.
15. Haffner SM, Rulope L, Dahlof B, Abadie E, Kupfer S, Zannad F. Metabolic syndrome, new onset diabetes, and new end points in cardiovascular trials. *J Cardiovasc Pharmacol* 2006, 47:469-475.
16. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. Report of a WHO/IDF Consultation. Geneva, World Health Org., 2006.
17. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European Cohorts. *Diabetes Care* 2003, 26:61–69.
18. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, 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, 53:2087-2094.
19. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, 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, 73:460-468.
20. Ohlson LO, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985, 34:1055-1058.
21. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998, 280:1843-1848.
22. Carr MC, Brunzell JD: Abdominal obesity and dyslipidemia in the metabolic syndrome. importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *J Clin Endocrinol Metab* 2004, 89:2601-2607.
23. Underwood PM. Cardiovascular risk, the metabolic syndrome and the hypertriglyceridaemic waist. *Curr Opin Lipidol* 2004, 15:495-497.
24. Yudkin JS. Adipose tissue, insulin action and vascular disease: inflammatory signals. *Int J Obes Relat Metab Disord* 2003, 27(Suppl 3):S25-28.

25. Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001, 21:961-967.

26. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003, 107:391-397.

27. Martínez MA, Puig JG, Mora M, Aragón R, O'Dogherty P, Antón JL, et al. MAPA (Monitorización Ambulatoria de la Presión Arterial) Working Group. Metabolic syndrome: prevalence, associated factors, and C-reactive protein: the MADRIC (MADrid Riesgo Cardiovascular Study). *Metabolism* 2008, 57:1232-1240.

28. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2003, 168:351-358.

29. Wang J, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. *Eur Heart J* 2007, 28:780-781.

30. Gale EA. The myth of the metabolic syndrome. *Diabetologia* 2005, 48:1679-1683.

31. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic Medicine* 2002, 19:708-723.

32. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 1999, 22.