BANTAO Journal 2009; 7 (1): 12-16

BJ

BANTAO Journal

Review

Metabolic Syndrome and Chronic Kidney Disease

Gjata Margarita[1], Nelaj Ergita[1], Gjergji Zheni [2], Koroshi Alketa [2] and Tase Mihal [1]

[1]Service of Internal Medicine and HTA, [2]Service of Nephrology and Hemodialysis, University Hospital Centre "Mother Teresa", Tirana, Albania

Abstract

The metabolic syndrome, which is characterized by obesity, serum lipid profile alterations, hypertension, and fasting hyperglycemia, is very common in developed countries, and its prevalence is likely to increase. Patients with a combination of risk factors, known as metabolic syndrome, are at an elevated long term risk of developing chronic kidney disease (CKD).

The definition of the metabolic syndrome identified 3 potential etiologic categories: 1-Central obesity and dyslipidemia, 2-Insulin resistance and glucose intolerance and 3-Leptin deficiency. Many inflammatory cytokines that are secreted by adipose tissue, including leptin, IL-6, TNF-α, and adiponectin, may be involved at least partially in promoting renal impairment, in particular the high plasma leptin levels that are observed in obesity may predispose to glomerulosclerosis.

The studies confirm that hypertension and fasting plasma glucose levels are associated with greater risk for microalbuminuria and a low glomerular filtration (GRF). Leptin increases sympathetic nerve trafficking and renal sodium retention, which may cause hypertension. Furthermore, it stimulates oxidative stress in endothelial cells and induces a proinflammatory state and also promotes atherosclerosis. Atherosclerosis and endothelial dysfunctions are other potential mechanisms by which leptin may affect renal structure and function. High levels of Renin-angiotensin-aldosterone-system activation promote glomerulosclerosis and tubulointerstitial injury.

Treatment consists of lifestyle modifications along with optimal control of blood pressure, blood sugar and lipids.

Keywords: Chronic kidney disease, metabolic syndrome, obesity, insulin resistance

Introduction

The metabolic syndrome, which is characterized by obesity, serum lipid profile alterations, hypertension, and fasting hyperglycemia, is very common in developed countries, and its prevalence is likely to increase [1]. The metabolic syndrome is a risk factor for the development of diabetes and cardiovascular disease; however, no prospective studies have examined the metabolic syndrome as a risk factor for chronic kidney disease (CKD). Patients with a combination of risk factors known as metabolic syndrome are at an elevated long term risk of developing chronic kidney disease (CKD). CKD risk was 43% higher in subjects, with at least 3 of the 5 characteristics of metabolic syndrome [2,3]. Metabolic syndrome occurs in nearly one of three patients with advanced CKD [4].

The aim of this paper is to revue the metabolic syndrome mechanisms that influence the onset and progression of CKD, and also the most effective measures of its prevention and treatment.

Definitions of metabolic syndrome

Various definitions of the syndrome have been proposed since its first description. The guidelines of the 2001 National Cholesterol Education Program - Adult Treatment Panel III [2] now are widely used to identify it, although a recent report from National Heart, Lung and Blood Institute and the American Heart Association (NHLBI/AHA) [5] recommended lowering the cut-off point for fasting blood glucose levels and abdominal obesity in men and proposed diagnosing the syndrome in the presence of only two of the defined criteria [5] (Table 1). The prevalence of metabolic syndrome varies widely according to the geographical location, race, gender, and urbanization, ranging from a low of 8% in French males to a high of 60% in the female Native Americans [6]. In India, the prevalence is 15-20%. South Asians are at a greater risk for developing complications as compared to Americans.

Pathogenesis of Metabolic Syndrome

The definition of the metabolic syndrome identified 3 potential etiologic categories: 1-Central obesity and dyslipidemia, 2-Insulin resistance and glucose intolerance and 3-Leptin deficiency.

1-Central obesity and dyslipidemia. Adipose tissue is recognized as a source of several molecules that are

Correspodence to: Margarita Gjata ,Service of Internal Medicine and HTA, University Hospital Center "Mother Teresa", Tirana, Albania Email: mresuli@yahoo.com

Table 1. NCEP-ATP III diagnostic criteria for metabolic syndrome and revised criteria as proposed by NHLBI/AHA

Parameter	NCEP-ATP III (2)	NHLBI/AHA (3)
Waist circumference (cm)		>94 in men
	>88 in women	>88 in women
Serum triglycerides (mg/dl)	≥150	≥150
Serum HDL cholesterol (mg/dl)	<40 in men	<40 in men
	<50 in women	<50 in women
Bìood pressure (mmHg)	≥130/85	≥130/85
Fasting plasma glucose (mg/dl)	≥110	≥100
No. of criteria needed for diagnosis	3	2

NCEP-ATP III, National Cholesterol Education Program—Adult Treatment Panel III; NHLBI/AHA: National Heart, Lung, and Blood Institute and American Heart

potentially pathogenic: excess nonesterified fatty acid, cytokines (tumor necrosis factor-α), resistin, adiponectin, leptin, and PAI-1. Visceral adipose tissue may be particularly active in producing several types of these factors [7]. However, the mechanisms underlying the association between abdominal obesity (particularly visceral obesity) and the metabolic syndrome are not fully understood and likely are complex. It has been assumed that obese adipose tissue releases an excess of fatty acids and cytokines that induce insulin resistance [8].

Combined hyperlipidemia is a hallmark of metabolic syndrome. The characteristic lipid disorders seen in this syndrome are hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C) and, often, normal levels of low-density lipoprotein cholesterol (LDL-C), although the LDL-C particles are typically smaller and more dense than usual. Whether these small, dense LDL-C particles increase cardiovascular risk independently of that related to hypertriglyceridemia and low HDL-C levels is uncertain [9,10]. The diagnosis of dyslipidemia is best made when a patient is in a basal state, without acute illness. Low HDL-C levels (<40 mg/dL in men, <50 mg/dL in women) are altered little by fasting. However, triglyceride concentration can rise substantially after food intake, and current diagnostic criteria are based on measurements obtained after 12 hours of fasting [5].

2-Insulin resistance and glucose intolerance. Insulin resistance is widely believed to be at the heart of the metabolic syndrome, even though there is as yet little clinical trial evidence that a reduction in insulin resistance will substantially improve any of the components of the metabolic syndrome other than glucose intolerance. This is not to say that insulin resistance per se does not play a significant role in implementing of metabolic syndrome [11]. When insulin-resistant muscle is already overloaded with lipids from high plasma nonesterified fatty acids levels (NEFA), some excess NEFA presumably are diverted to the liver, promoting fatty liver and atherogenic dyslipidemia [13]. Hyperinsulinemia may enhance output of very-low-density lipoprotein triglycerides, raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver. (14) Some data support the concept that insulin resistance or its associated hyperinsulinemia are independent risk factors for CVD, but this association has not yet been confirmed in controlled studies [15,16].

Elevated fasting glucose levels are an important feature of metabolic syndrome, but neither impaired fasting glucose, nor diabetes is an absolute criterion. Insulin resistance is associated with an increased risk of type 2 diabetes, and overt diabetes develops in many persons with metabolic syndrome [17,18].

3-Leptin deficiency. The role of leptin in controlling energy homeostasis is increasingly well defined, but it remains unclear whether leptin plays a role in the inflammatory syndrome caused by abdominal obesity. Clearly, serum leptin concentrations rise in proportion to body adiposity; therefore, obese individuals with the metabolic syndrome generally have higher circulating leptin concentrations [19]. However, obese individuals seem to be resistant to the hypothalamic effects of leptin; therefore, the catabolic pathways designed to reduce appetite and increase energy expenditure are not activated and excess body weight is maintained. Therefore, chronically elevated concentrations of leptin, as seen in obese individuals, may potentially predispose to progression of atherosclerosis [20]. Increased serum leptin concentrations, through direct effects on the immune system, clearly may trigger a proinflammatory state, as yet only circumstantial data from rodent studies suggest that this cytokine contributes to the chronic low-grade inflammation associated with the metabolic syndrome [21]. Leptin deficiency or resistance is associated with triglyceride accumulation in the liver and muscles due to inability of leptin to activate adenosine monophosphate (AMP) kinase in muscles [22].

Metabolic Syndrome as a risk factor for chronic renal disease

The metabolic syndrome has recently emerged as strong independent risk factor for CKD and end-stage renal disease. (23) Many inflammatory cytokines that are secreted by adipose tissue, including leptin, IL-6, TNF-α, and adiponectin, may be involved at least partially in promoting renal impairment, in particular, the high plasma leptin levels that are observed in obesity may predispose to glomerulosclerosis [25,31].

A large renal pathology study demonstrated that obesity-related glomerulopathy, which is characterized by focal segmental glomerulosclerosis and glomerulomegaly, increased in incidence from 0.2 to 2% of all biopsy diagnoses during the 15-yr period of the study [26]. None of the patients demonstrated a histological

pattern consistent with diabetic nephropathy, the presumed pathology associated with the metabolic syndrome. These studies raise the possibility that obesity, which is a cardinal feature of the metabolic syndrome, may lead to CKD. However, as mentioned earlier, this may be difficult to prove, in this case because obesity is also a risk for hypertension and diabetes [27].

Microalbuminuria is a clinical criterion for metabolic syndrome by the WHO classification. The frequency of microalbuminuria increases across the spectrum from those with normal glucose tolerance (5–10%), to metabolic syndrome (12–20%), to type 2 diabetes (25–40%). (10) Many patients presenting metabolic syndrome are hypertensive and/or have diabetes, well-known risk factors for the development and progression of CKD [28]. The studies confirm that hypertension and fasting plasma glucose levels are associated with the greatest risk for microalbuminuria and a low GRF [30].

Chen et al.observed that increased waist circumference significantly correlated with microalbuminuria and GRF decline, suggesting that obesity may be an independent risk for CKD [29,32].

Adipose tissue is a source of cytokines that produce endothelial dysfunction, and leptin may also affect the kidney indirectly [31]. It increases sympathetic nerve trafficking and renal sodium retention, which may cause hypertension. Furthermore, it stimulates oxidative stress in endothelial cells and induces a proinflammatory state and also promotes atherosclerosis. Atherosclerosis and endothelial dysfunctions are other potential mechanisms by which leptin may affect renal structure and function [21,27].

In the metabolic syndrome, hyperleptinemia, possibly hyperinsulinemia, insulin resistance activated sympathetic stimulation and both hemodynamic alterations, including interference with renal blood flow as a result of compression of the renal hilum and/or renal parenchyma by visceral are the main mechanism for activate renin-angiotensin-aldosterone system [33]. Renin-angiotensin-aldosterone system activation promotes glomerulosclerosis and tubulo-interstitial injury [34].

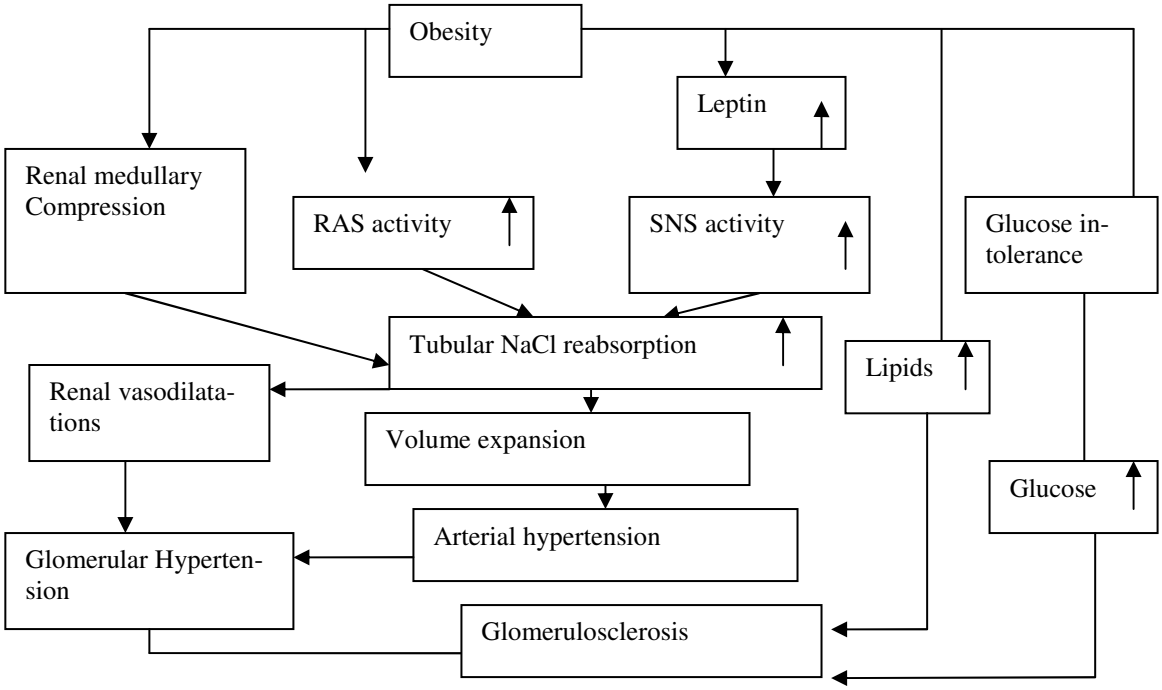

Fig. 1. Mechanisms by which obesity, glucose intolerance and lipids promote glomerulosclerosis

Several studies have examined the association between insulin resistance and risk for chronic kidney disease. A cross-sectional survey of 934 nondiabetic Native Americans found that the insulin resistance syndrome was associated with microalbuminuria [36].

Dyslipidemia may be an important factor in the development and progression of CKD [17]. Observational data and a recent meta-analysis suggest that elevated triglycerides and low HDL are independent risk factors for the development or acceleration of CKD and that the use of statins may slow CKD progression.

Muntner and colleagues found that high serum triglyceride and low HDL cholesterol levels predicted an increased risk for renal dysfunction in 12 728 participants in the Atherosclerosis Risk in Communities study [37]. A recent meta-analysis of clinical trials indicates that lipid lowering preserves glomerular filtration rate and decreases proteinuria level in patients with renal disease [38].

Mechanisms by which obesity, glucose intolerance and lipids promote glomerulosclerosis are presented in Figure 1.

Treatment of metabolic syndrome

The first step in the management of the metabolic syndrome is to control underling modifiable risk factors, principally obesity, physical inactivity, and an athero-

genic diet. Obesity guidelines insist on weight reduction through behavioral changes aimed to reduce caloric intake and increase physical activity, in order to achieve a 7–10% weight loss over 6–12 months [39-41].

Statins are widely used to reduce the risk of cardiovascular events. Fibrates more specifically target atherogenic dyslipidemia by significantly reducing plasma TG levels and moderately increasing HDL-C concentrations, but the efficacy of fibrates alone in reducing CVD events has not yet been substantiated, particularly among individuals with type2 diabetes [42,43]. The combined use of statin and fibrates produces the most beneficial effects on all lipid parameters and may result in the greatest improvement in CVD risk status [42].

Antihypertensive drugs are often required in addition to lifestyle changes to reach blood pressure goals. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are often the first-line therapy suggested [44].

Metformin, thiazolidinediones and acarbose are used in the treatment of type 2 diabetes. Studies have investigated their efficacy to prevent diabetes in individuals with impaired glucose tolerance and impaired fasting glucose, and they have shown that these drugs are effective at delaying type 2 diabetes onset.

Recently Rimonabant, a cannabinoid receptor type-1 antagonist, has shown promising results in type 2 diabetics as well as nondiabetics with obesity [45].

In conclusion, treatment consists of lifestyle modifications along with optimal control of blood pressure, blood sugar and lipids.

Conflict of interest statement. None declared.

References

1. Bakker SJL, Gansevoort RT, Zeeuw D. Metabolic syndrome: A fata morgana? *Nephrol Dial Transplant* 2007; 22: 15-20.
2. 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.
3. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, *et al*. Glomerular hyperfiltration: A new marker of metabolic risk. *Kidney Int* 2007; 71: 816-21.
4. Nelaj E; Gjata M; Lilaj L; Burazeri G; Sadiku E; Bare O; Tase M. Factors of cardiovascular risk in patients with type 2 diabetes and incipient nephropathy. *Hippokratia* 2008; Vol 12: 222-224.
5. Chen J, Muntner P, Hamm L, Jones DW, Batuman V, Fonseca V, *et al*. The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 2004; 140: 167-74.
6. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome: A new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabetic Med* 2006; 23: 469-80.
7. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. *JAMA*. 2002; 287: 356–359.
8. Despres JP, Golay A, Sjostrom L. Effects of Rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Eng J Med* 2005; 353: 2121-34.
9. Miranda, PJ; Defronzo, RA; Califf, RM; Guyton, JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. *Am Heart J* 2005; 149: 33–45.
10. Ayyobi AF, Brunzell JD. Lipoprotein distribution in the metabolic syndrome, type 2 diabetes mellitus, and familial combined hyperlipidemia. *Am J Cardiol* 2003; 92: 27–33.
11. Bjornheden T, Babyi A, Bondjers G, Wiklund O. Accumulation of lipoprotein fractions and subfractions in the arterial wall, determined in an in vitro perfusion system. *Atherosclerosis* 1996; 123: 43–56.
12. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; 278: F817-22.
13. Brent E, Wisse The Inflammatory Syndrome: The Role of Adipose Tissue Cytokines in Metabolic Disorders Linked to Obesity. *J Am Soc Nephrol* 2004; 15: 2792–2800.
14. Ginsberg HN, Zhang YL, Hernandez-Ono A. Metabolic syndrome: focus on dyslipidemia. *Obesity (Silver Spring).* 2006; 14: 41S–49S.
15. Balkau B, Charles MA, Drivsholm T, *et al*. European Group for the study of insulin resistance (EGIR). Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. Diabetes Metab 2002; 28: 364–76.
16. Toshiro Fujita. Insulin resistance and salt-sensitive hypertension in metabolic syndrome. *Nephrology Dialysis Transplantation* 2007; Vol 22, 11: 3102-3107.
17. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 2001; 86: 713–18.
18. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; 14: 173–194.
19. Weidmann P, de Courten M, Bohlen L. Insulin resistance, hyperinsulinemia and hypertension. *J Hypertens* 1993; 11 (suppl 5): S27–S38.
20. Stenvinkel P. Leptin and its clinical implications in chronic renal failure. *Miner Electrolyte Metab* 1999; 25: 298-302.
21. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis* 2002; 39: 1-11.

22. Mantzoros CS. Leptin in renal failure. *J Ren Nutr* 1999; 9(3): 122-5.
23. Alberti KG. Leptin and other components of the metabolic syndrome in Mauritius – a factor analysis. *Int J Obes Relat Metab Disord* 2001; 25: 126–131.
24. Sowers JR. Metabolic risk factors and renal disease. *Kidney Int* 2007; 71: 719-20.
25. Chen J, Muntner P, Hamm L, Jones DW, Batuman V, Fonseca V, *et al*. The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 2004; 140: 167-74.
26. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int* 2001; 59: 1498-509.
27. (Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD: Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int* 2001; 59: 1498–1509.
28. Rosenbaum M, Leibel RL, Hirsch J: Obesity. *N Engl J Med* 1997; 337: 396–407.
29. Hao, Z, Konta T, Takasaki S, Abiko H, Ishikawa M, Takahashi T, *et al*. The association between microalbuminuria and metabolic syndrome in the general population: The Takahata study. *Intern Med* 2007; 46: 341-6.
30. Chen J, Gu D, Chen CS, Wu X, Hamm LL, Muntner P, *et al*. Association between the metabolic syndrome and chronic kidney disease in Chinese adults. *Nephrol Dial Transplant* 2007; 22: 1100-6.
31. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, *et al*. Glomerular hyperfiltration: A new marker of metabolic risk. *Kidney Int* 2007; 71: 816-21.
32. Rizvi, Ali A. MD, FACP.Cytokine Biomarkers, Endothelial Inflammation, and Atherosclerosis in the Metabolic Syndrome: *Emerging Concepts The American Journal of the Medical Sciences* 2009; 338 (4): 310-318.
33. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; 278: 817-822.
34. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, *et al*. Glomerular hyperfiltration: A new marker of metabolic risk. *Kidney Int* 2007; 71: 816-21.
35. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among no diabetic adults. *J Am Soc Nephrol* 2005; 16: 2134-40.
36. Toshiro Fujita. The Renin System, Salt-Sensitivity and Metabolic Syndrome. *J Renin Angiogenesis Aldosterone System Issue* 2006; 181-183.
37. Hoehner CM, Greenlund KJ, Rith-Najarian S, Casper ML, McClellan WM. Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. *J Am SocNephrol* 2002; 13: 1626-34.
38. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and riskof developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000; 58: 293-301.
39. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001; 59: 260-9.
40. National Institutes of Health: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. Bethesda, Md.: National Institutes of Health, National Heart Lung and Blood Institute, 2001 (NIH publication no. 01-3670). Accessed online March 18, 2004, at:
41. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care* 2003; 26: 557-62.
42. Grundy SM, Abate N, Chandalia M. Diet composition and the metabolic syndrome: what is the optimal fat intake? *Am J Med* 2002; 113(suppl 9B): 25S-29S.
43. Ginsberg HN. Treatment for patients with the metabolic syndrome. *Am J Cardiol* 2003; 91(7A): 29E-39E.
44. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383-93.
45. Despres JP, Golay A, Sjostrom L. Effects of Rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Eng J Med* 2005; 353: 2121-34.