Modern Medicine. 2016, Vol. 23, No. 1 : 54-59

Review

Metabolic Syndrome - Cardiovascular and Metabolic, Complex, Difficult to Quantify Risk Factor

Radu-Valentin Coltuc[1], Victor Stoica[2]

[1]„Witting" Clinical Hospital Bucharest, „Titu Maiorescu" University, Bucharest, Romania
[2]„Dr. I. Cantacuzino"Clinical Hospital, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

REZUMAT

Sindromul metabolic - factor de risc cardiovascular si metabolic, complex, dificil de cuantificat

Sindromul metabolic (SM) reprezintă o aglomerare de factori de risc cardiovasculari și metabolici, legați între ei, care împreună îndeplinesc criteriile unui sindrom. Prin prevalența ridicată la nivel mondial (≈25%) el a devenit o problemă importantă de sănătate publică. Inițial debutul acestuia s-a făcut ca un concept, ulterior s-a conturat ca un sindrom. Mai multe foruri medicale au emis diverse definiții, deși tendința este de a utiliza o definiție comună. SM are o importanță clinică deosebită prin faptul că el crește riscul cardiovascular (de 2 ori), crește riscul de debut al DZ tip 2 (de 5 ori) și se poate asocia cu alte boli (ficat gras, boala cronică renală, neoplasm, boli psihice etc.). De altfel, această aglomerare de factori de risc cardiometabolici este ea însăși un factor complex, multiplu, deocamdată greu cuantificabil, având în vedere că sunt implicați în patogenia SM și alți factori în afara celor din definiție (statusul protrombotic și proinflamator, LDLc, insulinorezistența etc.). El poate fi utilizat pentru evaluarea riscului global pe termen lung (>10 ani). Identificarea pacienților cu SM ajută la intervenția terapeutică asupra fiecărui factor din componența sa și, în final, conduce la ameliorarea riscului cumulat din SM în ansamblu.

Cuvinte cheie: sindrom metabolic,definiție,patogeneza complexă, factor de risc greu cuantificabil

ABSTRACT

Metabolic syndrome (MS) is a cluster of cardiovascular and metabolic risk factors, interconnected, which together meet the criteria of a sindrom. With a high prevalence worldwide (≈25%), it became an important public health issue. At the beginning it was a concept, later on it emerged as a syndrome. Several medical organisations have released different definitions, although the trend is to use a common definition. MS has a high clinical importance: it increases the cardiovascular risk (2 times), the risk of the onset of type 2 diabetes (5 times) and it may be associated with other diseases (fatty liver, chronic kidney disease, cancer, mental illness, etc.). Moreover, this cluster of cardiometabolic risk factors is itself a complex, multiple factor, yet hardly quantifiable, because in the pathogenesis of MS are involved in addition other factors besides those included in the definition (prothrombotic and proinflammatory state, LDLc, insulin resistance etc.). It can be used to assess the overall risk in the long term (>10 years). Identification of the patients with MS helps for therapeutic intervention on every factor from its component and finally leads to improvement in overall cumulative risk of MS.

Key words: metabolic syndrome, definition, complex pathogenesis, difficult to quantify risk factor

Corresponding author: Radu-Valentin Coltuc, M.D., Ph. D. Candidate
Witting Clinical Hospital Bucharest, Bucharest, Romania e-mail: valentin_drv@yahoo.com

INTRODUCTION

MS is a clinical and pathological entity, characterized by a cluster of related clinical, anthropometric and biochemical features such as abdominal obesity, hyperglycemia, dyslipidemia and hypertension. (1) The importance of MS results from the fact that its component factors increase cardiovascular risk (2), are a strong predictor of occurrence of type 2 diabetes (3), generate fatty liver (4) and also increase all-cause mortality. (5)

Epidemiological data

MS prevalence has increased greatly in recent decades, especially in developed countries, which also led to increased risk of cardiovascular morbidity and mortality. Both factors, genetic and environmental, contribute to it. Globally, a quarter of the adult population (between 20% and 30%) have this syndrome, with variations depending on geographic region, age, dietary habits and genetics. In the US the prevalence of MS is around 22% in some studies, up to 39% in others. This varies by the definition used for MS (higher prevalence for the criteria IDF, compared with NCEP), by ethnicity and potentially modifiable lifestyle factors (BMI, smoking, low household income, increased intake of carbohydrates, physical inactivity etc.). The high proportion of worldwide MS has become a epidemic disease. (6.7)

The pathophysiology of MS is a complex process with multiple interconnected mechanisms.

MS is the result of an interaction between genetic and environmental factors.

A. Genetic factors are under investigation. It is anticipated that several genes that encode energy storage information, exposed to the environmental factors (atherogenic food, sedentary lifestyle, etc.), can cause the phenotype of SM with obesity and hyperglycemia.

B. Environmental factors, by far the most studied and most important factors involved in etiopathogenesis MS, are insulin resistance and central obesity. Other factors are: hypertension, atherogenic dyslipidemia, proinflammatory status, prothrombotic status, age and others under analysis.

Insulin resistance is one of the essential factors of MS. Adipose tissue releases esterified fatty acids and leads to insulin resistance. Hyperinsulinemia may increase synthesis of very low-density lipoprotein triglycerides. Insulin resistance can raise arterial pressure. If initially disruption of insulin activity is compensated by changing insulin secretion and clearance, afterwards these mechanisms are outdated and hyperglycemia occurs. (8)

Central obesity is a metabolically active tissue that contributes to the development of other components of MS. It plays an endocrine organ that releases numerous cytokines in circulation. Excess body fat can decrease adipose tissue perfusion, with consequent hypoxia, which in turn stimulates the production of biologically active metabolites, called adipocytokines (glycerol, free fatty acids, leptin, PAI-1, PCR and inflammatory mediators (TNF alpha, IL-6)). All these lead to a systemic inflammation. (9)

The two mechanisms dispute their supremacy as the main mechanism, depending on the arguments of the different authors.

Hypertension is a classic component of the definition of MS. Up to one third of hypertensive patients have this syndrome. The arterial pressure value is strongly associated with abdominal obesity and insulin resistance, important pathophysiologic factors of MS. The main mechanisms presumed to cause hypertension are: visceral obesity, insulin resistance, oxidative stress, endothelial dysfunction, activated renin-angiotensin system, increased inflammatory mediators and obstructive sleep apnea. (10)

Atherogenic dyslipidemia is characterized by small, dense particles of LDLc, high TG and low HDLc and means an increased risk of atherosclerotic disease.

Proinflammatory state. Adipose tissue releases inflammatory cytokines that create a state of generalized inflammation, contributing to insulin resistance and higher cardiovascular risk. (11)

Central obesity promotes prothrombotic status by altering the intrinsic and extrinsic coagulation, fibrinolysis and platelet function. Adipocytokines synthesized by adipose tissue are involved, which means that between inflammation and thrombosis there is a close connection. (12)

Smoking. Heavy smokers have a significant risk of developing MS and of association with atherogenic dyslipidemia, and smoking cessation would reduce it by 35-55%. (7)

Physical inactivity is associated with abdominal obesity and high waist circumference, with all the consequences resulting therefrom. (7).

Concluding, knowledge of the pathophysiology of MS is important because it helps to identify patients with an increased risk of cardiovascular disease and type 2 diabetes. (8)

Metabolic syndrome history

MS started out as a concept, later emerged as a syndrome. (9)

250 years ago the Italian anatomist Morgagni had observed the frequent association between central obesity, atherosclerosis and gout. In 1923 a Swedish physician Kylin has shown an association between high blood pressure, diabetes and gout. In 1965 Crepaldi and Avogaro had brought the concept of "plurimetabolic syndrome", which included: obesity, dyslipidemia, hypertension and diabetes. (1)

Reaven in 1988 noted that some metabolic risk factors (dyslipidemia, hypertension, hyperglycemia) are crowded together and constitute a multiplied risk factor for

cardiovascular disease. This cluster was called syndrome X. Reaven has the merit to introduce the concept of insulin resistance. A year later, Kaplan added obesity and renamed it as “The Deadly Quartet” (abdominal obesity, glucose intolerance, hypertriglyceridemia and hypertension), and then, in 1992, to be renamed "insulin resistance syndrome". (9)

So, since 1988 it is used the term of metabolic syndrome, although it would be more correct the term of dysmetabolic syndrome. (1)

The definition of metabolic syndrome

The first definition of MS was developed by the WHO in 1998 and included insulin resistance or impaired glucose tolerance or type 2 diabetes as an essential component, together with at least two of the following parameters: increased blood pressure, hypertriglyceridemia and / or increased HDL, obesity or microalbuminuria. Afterwards appeared many definitions issued by various medical organisations. The EGIR excluded microalbuminuria from the definition. In 2001, the NCEP / ATPIII has drafted a new set of criteria that included waist circumference, blood lipids, blood pressure and glucose. So insulin resistance was no longer among the parameters. Later in 2005, the IDF has developed a new definition of MS in which parameters have been specified more precisely to be used in research studies. Abdominal obesity, with waist circumference measurement as a screening of its detection, was introduced as a condition for the diagnosis of MS. It was also adopted by the AHA / NHLBI. So the AACE,WHO and the EGIR definitions are focused on insulin resistance and the NCEP / ATPIII and IDF on waist circumference. Currently the most common definitions are those of the NCEP / ATPIII and the IDF. (5, 13)

Analysing five different diagnostic criteria for the MS in patients with T2DM, in an article published in the Indian Journal Endocr. Metab. in 2014, it was concluded that, using the WHO criteria as the gold standard for the diagnosis of the MS, a good performance for the IDF criteria is demonstrated, because of its ease of application and its level of agreement with the WHO criteria and recommends the IDF criteria for screening of the MS in people with T2DM. (14) An original study published in 2010 showed that the risk factors for the MS in patients with T2DM depend of the criteria used to define MS, supporting the need for a single clinical and epidemiological useful definition. (15)

Moreover, in 2009 several medical organizations as the IDF, the NHLBI, the AHA, the WHF, the IAS, the IASO, tried bringing together all definition diagnostic criteria into a common definition, in which no component was longer mandatory. The MS diagnosis is present if at least 3 of the following parameters are present:

- Increased waist circumference (according to population and specific ethnicity);
- Triglycerides ≥ 150 mg/dl or treatment for them;
- HDL < 40 mg/dL in men and 50 mg/dL in women or specific treatment;
- blood pressure ≥ 130/85 mmHg or specific treatment;
- Glycemia ≥ 100 mg/dl or known T2DM. (16)

The metabolic syndrome - a predictor for cardiovascular disease (CVD) and type 2 diabetes mellitus

Since the discovery of the MS, there were numerous trials or post-hoc analysis showing what it was supposed: a cluster of cardiovascular and metabolic risk factors, as the metabolic syndrome as a whole, it is also a risk factor. The difficulty comes when we have to specify the overall risk of the MS. It is important to have a common and exact definition of the MS, because it could be used as a tool for quantifying the risk for cardiovascular and T2DM.

A patient with MS has, on average, three-fold risk of a heart attack or stroke, two-fold risk of CVD or dying from such events, and five-fold greater risk of developing type 2 diabetes mellitus in both sexes when compared with people without it. (17) One problem was to demonstrate that the risk of cardiac events in patients with the MS is greater than the simple sum of the individual components. It seems that the hypothesis is partially confirmed, with some nuances. Therefore, a recent large multiethnic study, INTERHEART, showed that the presence of MS is associated with a >2.5 - fold increase in the risk of acute myocardial infarction (AMI), MI risk has increased if more component factors of MS were present. However, the risk in the patient with the MS seems not to be higher than the risk of major individual components such as T2DM and hypertension. (5) In another recent study, prospective, observational, of over 27 000 consecutive patients, who underwent CT Angiography between 2003 and 2009, the CONFIRM study, it was observed that the prevalence and the severity of coronary artery disease and risk of MACE were significantly elevated in patients with the MS compared to those with only one component of the MS, but not for those with two components. (18)

In a study published in 2010 in "Journal of Diabetes and its Complications" there were analysed three sets of criteria (WHO, NCEP and IDF) in predicting cardiovascular risk. It was shown that IDF criteria were appropriate in predicting cardiovascular risk in women, while those of NCEP III were more suitable in men. The best components to identify cardiovascular risk were hypertension and cut-off point of waist circumference in women, defined by IDF criteria, and triglycerides defined by IDF criteria in men. (19)

Besides cardiovascular risk, the MS predispose to the emergence of type 2 diabetes. Various studies and meta-analyses have shown that MS is not simply a risk factor for diabetes, it is associated with an approximately 5-fold greater than type 2 diabetes. Thus SM becomes an

important predictor for the onset of type 2 diabetes in many different populations. Simple measurements such as BMI, FPG and HbA1c could predict correctly a type 2 diabetes in these patients. (20)

Although MS increases the likelihood of cardiovascular disease or type 2 diabetes, risk cannot be estimated exactly because it involves other factors besides those from definition of MS, such as age, smoking, gender, endothelial dysfunction, LDLc, proinflammatory and prothrombotic state etc. (5)

In the elderly there were some studies (Prosper-Prospective Study of Pravastatin in the Elderly at Risk and BRHS - The British Regional Heart Study) which showed that MS and its components, especially FPG, are associated with type 2 diabetes, but have weak or no association with vascular risk in elderly population. (21)

Analysing data from NHANES (National Health and Nutrition Examination Survey) between 1999-2010 it was found that the use of multiple biomarkers (eg.: PCR, fasting blood glucose, TG, HDLc etc.) in a single multivariate model can provide high accuracy cumulative risk assessment for each cardiovascular disease. (22)

The diagnosis of MS is a tool for assessment of cardiovascular risk, together with established risk scores, as Framingham, PROCAM, SCORE risk map of the European Society of Cardiology etc. An interesting study published in 2013 in Germany included patients undergoing intervention of corporal weight reduction. In one analysis, in patients older than 40 years with or without MS, it was calculated at the beginning and end of the study, cardiovascular risk score using the SCORE risk tables. It was noted that this assessment may underestimate risk in patients with MS, where it would be useful to assess the combined risk factors in the SM. Current recommendations are that traditional risk scores (Framingham, SCORE etc.) to be used for short-term assessment of cardiovascular risk (<10 years), while identifying individuals with MS is more accurate in predicting cardiovascular and metabolic risk in the long term (>10 years). (23)

Besides heart disease and type 2 diabetes, MS may be associated with other pathologies:

- With cancer. There have been studies that have shown that MS may increase the risk of cancer and patients with these two pathologies also have higher mortality from cancer. (13)
- With chronic kidney disease (CKD). MS, with its components lead to CKD. Hyperinsulinemia, activation of the rennin-angiotensin-aldosterone system, oxidative stress increase of oxidative stress, and inflammatory cytokines are mechanisms involved. Albuminuria is a good marker of MS-related renal injury. (24)
- With psychosocial disorders. MS may be associated with schizophrenia and depression. (7)
- With atrial fibrillation. Obesity increases the risk of atrial fibrillation, regardless of presence of MS, while overweight and abdominal circumference were associated with it, only if MS was present. (25)
- With non-alcoholic fatty liver with disease (NAFLD). Abdominal obesity, insulin resistance, dyslipidemia and hyperglycemia are involved in the pathogenesis of NAFLD. (4)

In the literature there are mentioned and other associations: with polycystic ovarian disease, sleep apnea, psoriasis, erectile dysfunction etc. (7)

So MS is a multiplied, complex cardiovascular and metabolic risk factor, yet hardly quantifiable considering that its complicated pathogenesis involves other risk factors besides those included in the definition (ex. proinflammatory state, prothrombotic state, insulin resistance, smoking, etc.) (5)

The management of metabolic syndrome

It is the unanimous opinion of the authors that MS prevention or amelioration of risk components within it always starts with the establishment of a proper lifestyle. If certain risk factors for MS, as dyslipidemia, type 2 diabetes, hypertension, could be controlled mainly with proper treatment (besides lifestyle change), other factors component could be influenced just by lifestyle modification. The main non-pharmacological measures are:

- Daily physical activity for 30-60 minutes of moderate-intensity aerobic activity.
- Reduction in fat intake, diet rich in fresh fruits, high fibre, whole grain and vegetables.
- Reducing weight
- Smoking cessation
- Reducing excessive alcohol consumption (26).

Non-pharmacological measures amending lifestyle are important in both preventing MS and in regression of the MS component parts.

Early identification of the metabolic abnormalities and appropriate intervention by instituting holistic, multidisciplinary preventive measures at an individual, community or society could contribute to the establishment of healthy eating habits and combating of the sedentary lifestyle by physical activity, which would reduce the epidemic of MS. (17). Other authors have shown that interactive web program is beneficial for people with MS, in improved management of metabolic syndrome and adoption of a healthy lifestyle. (27)

CONCLUSION

Between experts who considered MS as a simple cluster of cardio-metabolic risk factors and those who said it is more than an association, met the criteria of a syndrome there was a real debate. In recent years more and more authors agree that central obesity, atherogenic dyslipidemia, hyperglycemia and hypertension, are closely interrelated and influence each other forming a syndrome.

Clinical importance of this syndrome results in the fact that it incorporates a significant risk for cardiovascular events (approximately 2-fold), is highly predictive of the onset of type 2 diabetes (risk 5 times) and is associated with other pathologies (chronic kidney disease, mental illness, sleep apnea, fatty liver disease, psoriasis etc.). It is primarily an indicator of long-term risk (>10 years). Current recommendations are that therapeutic intervention should be over each factor and not on the whole SM. One difficulty is accurate quantification of risk contained in the diagnosis of MS, considering that in its complex pathogenesis other factors (proinflammatory state, prothrombotic state, insulin resistance, smoking, etc.) are involved than classic definition components.An early intervention of all modifiable risk factors is key for prevention and amelioration of the cumulative risk in the MS.

Abbreviations

AACE - American Association of Clinical Endocrinology, AHA/NHLBI - American Heart Association / National Heart, Lung, and Blood Institute, BMI-Body Mass Index, CONFIRM - The Coronary CT Angiography evaluation for Clinical Outcomes: An Interventional Multicenter Registry, DM - Diabetes mellitus, EGIR - European Group for study of Insulin Resistance, FPG - Fasting plasma glucose, HDL - High Density Lipoprotein, IAS - International Atherosclerosis Society, IASO - International Association for the Study of Obesity, IDF - International Diabetes Federation, LDLc - Low Density Lipoprotein Cholesterol, MACE - Major adverse cardiovascular events, MS - metabolic syndrome, NCEP - ATP III: National Cholesterol Education Program - Adult Treatment Panel III, TG - triglycerides, US-United States, WHF - World Heart Federation, WHO - World Health Organization.

Acknowledgement

This material is part of a study of the PhD thesis, currently under development by COLTUC RADU VALENTIN, Ph. D. Candidate at the UMF CAROL DAVILA with Prof. STOICA VICTOR as thesis coordinator. The thesis has the following title: “Rolul statinelor asupra funcției renale la pacienții hipertensivi și cu sindrom metabolic”.

REFERENCES

1. Șuța R. S., Șuța C. Metabolic syndrome – a risky combination. ARS MedicaTomitana. Volume 18, Issue 4, Pages 188–192, ISSN (Online) 1841-4036.
2. Rhee SY, Park SY, Hwang JK, et al. Metabolic syndrome as an indicator of high cardiovascular risk in patients with diabetes: Analyses based on Korea National Health and Nutrition Examination Survey (KNHANES) 2008. Diabetology & Metabolic Syndrome. 2014;6:98.
3. Ford ES, Schulze MB, Pischon T, Bergmann MM, Joost H-G, Boeing H. Metabolic syndrome and risk of incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. Cardiovascular Diabetology. 2008;7:35.
4. Genel S, Aurelia C, Donca V, Emanuela F (2015) Is the Non-Alcoholic Fatty Liver Disease Part of Metabolic Syndrome? J Diabetes Metab 6:526.
5. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Medicine. 2011;9:48.
6. Nematy M, Ahmadpour F, Rassouli ZB, Ardabili HM, Azimi-Nezhad M (2014) A Review on Underlying Differences in the Prevalence of Metabolic Syndrome in the Middle East, Europe and North America. J Mol Genet Med S1:019.
7. Kelli HM, Kassas I, Lattouf OM (2015) Cardio Metabolic Syndrome: A Global Epidemic. J Diabetes Metab 6: 513.
8. Thaman RG, Arora GP. Metabolic Syndrome: Definition and Pathophysiology – the discussion goes on!. J. Phys. Pharm. Adv.. 2013; 3(3): 48-56.
9. Jaspinder Kaur, “A Comprehensive Review on Metabolic Syndrome,” Cardiology Research and Practice, vol. 2014, Article ID 943162, 21 pages, 2014.
10. Yanai H, Tomono Y, Ito K, Furutani N, Yoshida H, Tada N. The underlying mechanisms for development of hypertension in the metabolic syndrome. Nutrition Journal. 2008;7:10.
11. Timar R., Timar B., Degeratu D., Serafinceanu C., Oancea C. Metabolic syndrome, adiponectin and proinflammatory status in patients with type 1 diabetes mellitus. The Journal of International Medical Research. 2014;42(5):1131–1138.
12. Isabella Russo, “The Prothrombotic Tendency in Metabolic Syndrome: Focus on the Potential Mechanisms Involved in Impaired Haemostasis and Fibrinolytic Balance,” Scientifica, vol. 2012, Article ID 525374, 17 pages, 2012.
13. O'Neill, S. and O'Driscoll, L. (2015), Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obesity Reviews, 16: 1–12.
14. Onesi SO, Ignatius UE. Metabolic syndrome: Performance of five different diagnostic criterias. Indian Journal of Endocrinology and Metabolism. 2014;18(4):496-501.
15. Rodríguez A, Delgado-Cohen H, Reviriego J, Serrano-Ríos M. Risk factors associated with metabolic syndrome in type 2 diabetes mellitus patients according to World Health Organization, Third Report National Cholesterol Education Program, and International Diabetes Federation definitions. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2011;4:1-4.
16. Obokata M, Negishi K, Ohyama Y, Okada H, Imai K, Kurabayashi M. A Risk Score with Additional Four Independent Factors to Predict the Incidence and Recovery from Metabolic Syndrome: Development and Validation in Large Japanese Cohorts. Yang X-F, ed. PLoS ONE. 2015;10(7):e0133884.
17. Kaur J. Assessment and Screening of the Risk Factors in Metabolic Syndrome. Medical Sciences. 2014; 2(3):140-152.
18. Ahmadi A, Leipsic J, Feuchtner G, et al. Is Metabolic Syndrome Predictive of Prevalence, Extent, and Risk of Coronary Artery Disease beyond Its Components? Results from the Multinational Coronary CT Angiography Evaluation for Clinical Outcome: An International Multicenter Registry (CONFIRM). Lipinski M, ed. PLoS ONE. 2015;10(3):e0118998.
19. Somlak Chuengsamarna, Suthee Rattanamongkoulgulb, Alfredo Villarroel Association between metabolic syndrome and risk of cardiovascular disease, using different criteria and stratified by sex. International Journal of Diabetes Mellitus. doi:10.1016/j.ijdm. 2010.05.011

20. Ozery-Flato et al.: Predictive models for type 2 diabetes onset in middle-aged subjects with the metabolic syndrome. Diabetology & Metabolic Syndrome 2013 5:36.
21. Sattar N., McConnachie A., Shaper A. G., et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. The Lancet. 2008; 371(9628):1927–1935.
22. Coffman E, Richmond-Bryant J. Multiple biomarker models for improved risk estimation of specific cardiovascular diseases related to metabolic syndrome: a cross-sectional study. Population Health Metrics. 2015;13:7.
23. J. Willers and A. Hahn, "Risk Assessment Using Two Different Diagnostic Tools: Metabolic Syndrome and Cardiovascular Risk Score (SCORE)—Data from a Weight Reduction Intervention Study," Food and Nutrition Sciences, Vol. 4 No. 10, 2013, pp. 1028-1036.
24. Yi-Jing Sheen and Wayne Huey-Herng Sheu, "Metabolic Syndrome and Renal Injury," Cardiology Research and Practice, vol. 2011, Article ID 567389, 13 pages, 2011.
25. Nyström PK, Carlsson AC, Leander K, de Faire U, Hellenius M-L, Gigante B. Obesity, Metabolic Syndrome and Risk of Atrial Fibrillation: A Swedish, Prospective Cohort Study. Maeda N, ed. PLoS ONE. 2015;10(5):e0127111.
26. Mahmood D (2015) Management of Residual Cardiovascular Risk in Dyslipidaemic Patient with Metabolic Syndrome. Gen Med (Los Angel) 3:163.
27. Jahangiry L, Shojaeizadeh D, Abbasalizad Farhangi M, et al. Interactive web-based lifestyle intervention and metabolic syndrome: findings from the Red Ruby (a randomized controlled trial). Trials. 2015;16:418.