

Addressing Metabolic Syndrome In Family Practice: Screening Tools And Lifestyle Interventions

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Abstract

Background: Metabolic syndrome is a cluster of interrelated risk factors: central obesity, hypertension, dyslipidemia, and hyperglycemia that when present together raises the risk of cardiovascular disease and type 2 diabetes. There has been a global rise in the prevalence of metabolic syndrome running parallel to the rise in obesity. A broader impact on health is linked with metabolic syndrome as it has also been associated with other comorbidities like fatty liver, polycystic ovarian disease and certain cancers.

Objective: This review aims at addressing metabolic syndrome in family practice with detailed review of screening tools and lifestyle interventions.

Methodology: The review is comprehensive research of PUBMED and Google scholar from the year 2001 to 2024.

Conclusion: Clustering of various modifiable risk factors which when presented together pose a serious threat to health is termed as metabolic syndrome. Metabolic syndrome is screened by setting certain guidelines for obesity, blood pressure and other risk factors and adhering to the standard target ranges. Lifestyle modification is the mainstay for management of metabolic syndrome. Treating the risk factors individually by modifying lifestyle plays an important role in the management of metabolic syndrome. All the risk factors should be treated simultaneously. Lifestyle modification has proven to reverse metabolic syndrome if implemented on time. A multidisciplinary, team-based care model involving dietitians, exercise specialists, diabetes educators, and sometimes endocrinologists or cardiologists can enhance support for the patient and improve adherence.

Keywords: Metabolic syndrome, Cardiovascular disease, Central adiposity, Type 2 diabetes, DASH diet, Dyslipidemia.

Introduction

The coexistence of various metabolic abnormalities that appear together and increase an individual's risk for cardiovascular diseases and type 2 diabetes is termed Metabolic syndrome. Increased blood pressure, atherogenic dyslipidemia (characterized by high triglycerides and low HDL cholesterol), central obesity with insulin resistance, and hyperglycemia are the characteristic risk factors of metabolic syndrome. These factors, when clustered together as metabolic syndrome, confer a greater risk as compared to individual presentation, which in itself is very harmful. A 5 fold higher risk of developing type 2 diabetes and a twofold higher risk of developing cardiovascular disease have been reported in patients with metabolic syndrome.^[1] A broader impact on health is linked with metabolic syndrome as it has also been associated with other comorbidities like fatty liver, polycystic ovarian disease, and certain cancers.^[2]

Epidemiology

There has been a global rise in the prevalence of metabolic syndrome running parallel to the rise in obesity. Approximately 20-30% adults in the United States and other European countries meet the criteria for metabolic syndrome, and this prevalence increases with age. An early recognition and intervention in the family practice setting is necessary for metabolic syndrome because of the high prevalence and substantial prognosis. The amalgamation of risk factors that constitute metabolic syndrome is first diagnosed by the family physician, who can initiate early intervention, thereby reducing the chances of critical end-stage diseases like myocardial infarction and stroke. Different organizations have given different definitions and diagnostic criteria for metabolic syndrome, making it difficult to precisely address the disease. The common consensus is that metabolic syndrome, instead of being considered as an individual disease, should be considered as an amalgamation of modifiable risk factors. The sooner these risk factors are addressed and aggressively treated by lifestyle modifications, the better the outcome. This review aims to clarify the definition and screening tools of metabolic syndrome and set a clear outline for the lifestyle modifications required as first-line therapy of the disease.^[2]

Definition and Diagnostic Criteria of Metabolic Syndrome

The clinical presentation of metabolic syndrome includes a combination of risk factors above the defined thresholds. Three major definitions have been considered in this article: International Diabetes Federation (IDF), World Health Organisation (WHO) and National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) as summarised in table 1.^[3] All the three definitions include measures of obesity, blood pressure, glucose metabolism and blood lipids with the only difference being which factor is considered as an essential element. The WHO definition, which was given in 1999, had insulin resistance and/or glucose dysfunction as the mandatory component with hypertension, obesity, dyslipidemia, or microalbuminuria as the additional criteria. At least two of these additional criteria must be present to characterize metabolic syndrome. The NCEP ATP III definition was first given in 2001 and later modified in 2005, and required a minimum of three risk factors out of the five to be present. The IDF definition required central obesity as the prime risk factor with any two other risk factors. Constant efforts are being made to harmonize the criteria. A joint panel of European societies in 2022 modified the definition stating obesity as the primary driver along with two out of three risk factors, namely elevated blood pressure, impaired glucose regulation, and atherogenic dyslipidemia^[3]

Table 1. Diagnostic Criteria for Metabolic Syndrome (Selected Definitions)^[3]

Definition	Diagnostic Criteria for Metabolic Syndrome
NCEP ATP III (AHA/NHLBI, 2005) National Cholesterol Education Program	Any 3 of the following 5: (1) Waist circumference ≥ 102 cm in men or ≥ 88 cm in women; (2) Triglycerides ≥ 150 mg/dL; (3) HDL cholesterol < 40 mg/dL in men or < 50

	mg/dL in women; (4) Blood pressure $\geq 130/85$ mmHg (or on hypertension treatment); (5) Fasting glucose ≥ 100 mg/dL (or on hyperglycemia treatment).
IDF (2005) International Diabetes Federation	Central obesity is required (waist circumference ≥ 94 cm in Europid men or ≥ 80 cm in Europid women; lower cut-offs for some ethnic groups) plus at least 2 of the following: Triglycerides ≥ 150 mg/dL (or on treatment for elevated TG); HDL < 40 mg/dL in men or < 50 mg/dL in women (or on treatment for low HDL); Blood pressure $\geq 130/85$ mmHg (or on treatment for hypertension); Fasting glucose ≥ 100 mg/dL (or previously diagnosed type 2 diabetes).
WHO (1999) World Health Organisation	Insulin resistance or glucose dysregulation is required (type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose, or elevated insulin levels) plus at least 2 of the following: Blood pressure $\geq 140/90$ mmHg (or on hypertension treatment); Dyslipidemia – triglycerides ≥ 150 mg/dL and/or HDL < 35 mg/dL (men) or < 39 mg/dL (women); Obesity – BMI ≥ 30 kg/m ² or waist-to-hip ratio > 0.90 (men) or > 0.85 (women); Microalbuminuria – urinary albumin excretion ≥ 20 μ g/min or albumin:creatinine ratio ≥ 30 mg/g.

The NCEP ATP III and IDF criteria rely on simple clinical measurements and Lab tests, making them easier to apply in the primary care settings. Family physicians can identify these components during annual examinations. Measurement of Waist circumference is generally overlooked during clinical examinations. IDF guideline mandates measuring waist circumference during initial evaluation, and if an individual lies above the cut off, he should be assessed for other risk factors. It should be noted that even in the absence of the defined main risk factors, if patients present with any of the above risk factor combinations, they should be aggressively intervened. High-risk individuals should be tracked down using the definition of metabolic syndrome, and lifestyle modifications should be implemented by the care provider. ^[4]

Screening for Metabolic Syndrome in Family Practice

Screening for metabolic syndrome involves assessment of the risk factors. In the primary setting, risk factors are assessed by measuring abdominal circumference. Blood pressure evaluation, lipid profile evaluation, and glucose monitoring. Populations that are considered at risk should be evaluated for individual components. According to the U.S. preventive task force guidelines, all adults between the ages of 35 and 70 who are overweight should be screened for diabetes, and all who are diabetic or fall in the prediabetic category should be referred for immediate intervention. These individuals are at a higher risk for other metabolic syndrome features. Blood pressure monitoring should also be done at every visit in the primary care setting, and in cases where other abnormalities are seen, lipid profiles should also be assessed.

These factors, when identified early in the primary care settings, play a crucial role in the prevention of cardiovascular diseases and diabetes. ^[5]

In patients with elevated risk factors, targeted risk assessment tools can be used for a closer evaluation. Questionnaires like Finnish Diabetes Risk Score (FINDRISC) or the American Diabetes Association risk test can be used for screening insulin resistance or risk of diabetes by asking questions based on BMI, family history, and lifestyle. Cardiovascular risk calculators (such as the ACC/AHA Pooled Cohort Equations) can be used to stratify patients by 10-year heart disease risk. According to the USPSTF, metabolic syndrome itself is a risk factor and should be managed by early lifestyle modifications. It states that, for CVD prevention in patients with multiple risk factors like metabolic syndrome, early intensive intervention should be offered in primary care settings. All 5 risk factors of metabolic syndrome should be evaluated in patients with overweight and obesity by the family physician who can implement a checklist for the same in the electronic health record for annual visits. ^[6]

If a patient visiting the primary care setting presents with persistent hypertension, he should be evaluated for other risk factors like weight, abdominal circumference, and fasting labs for glucose and lipid should be obtained, screening for metabolic syndrome cluster. These readings can be fed in the clinical decision support tools, and if they meet the criteria for metabolic syndrome should be documented as an active problem, and management should be appropriately planned. Weight and BMI trajectories should be monitored for younger individuals with obesity and family history. Youth with a strong family history or obesity should be evaluated for diabetes and lipid disorders. If detected and intervened early with lifestyle modifications, a full-blown metabolic syndrome can be avoided in adulthood. Pediatric obesity has shown strong links to future metabolic syndrome and hence early lifestyle modifications offer a greater value. ^[7] Vigilance in screening of all the components of metabolic syndrome helps in early detection in family practice. If guideline-based screening protocols for obesity, diabetes, dyslipidemia, and hypertension are followed, primary care providers would be screening for metabolic syndrome. The key being recognition of clustering when a patient has multiple moderate abnormalities, the clinician should identify this as metabolic syndrome and a comprehensive management plan should be initiated. ^[7]

Lifestyle Interventions for Managing Metabolic Syndrome

The cornerstone for metabolic syndrome therapy is lifestyle modification. The first line of treatment for metabolic syndrome is lifestyle intervention focusing on weight loss, diet improvement and exercise. Metabolic health can be improved by addressing poor diet, excess adiposity and physical inactivity. Medications for managing diabetes and hypertension should be used as an adjunct and not as a replacement to healthy lifestyle changes. ^[7]

Weight Reduction

The most powerful intervention for metabolic syndrome in obese patients is weight loss. Insulin resistance, lipid abnormalities, and hypertension are generally seen in patients with central adiposity. A reduction of 5-10% of body weight in 6-12 months has shown positive effects in patients with metabolic syndrome. The Diabetes Prevention Program demonstrated that when approximately 7% body weight was lost through diet and exercise, a 58% reduction was seen in progression from prediabetes to diabetes. Modest weight loss (5-10%), which includes visceral fat reduction, has shown improvements in blood pressure, cholesterol, and triglycerides. Consequently, the contemporary guidelines from cardiology and endocrine societies set an initial weight-loss goal of around 7% for those with metabolic syndrome, with an ultimate aim of achieving a healthy BMI ($<25 \text{ kg/m}^2$) if possible. ^[6,7]

Weight reduction is accomplished by decreasing calorie intake. When a deficit of approximately 500Kcal is maintained daily, a loss of 0.5Kg per week has been observed. Behavioral strategies such as self-monitoring of food intake and body weight, goal-setting, and regular follow-up have proven effective. Nutritionists and health coaches with structured programs should be leveraged by primary care providers to support patients in the weight loss journey. Anti-obesity medications can be administered to patients with a BMI more than or equal to 30. Medications like GLP-1 receptor agonists have shown increased efficiency

in reducing weight. Bariatric surgery can also be effective in drastically reducing weight, and hence, patients should be evaluated by their primary care provider if they need surgical intervention. However, intensive lifestyle modifications remain the safest and most accessible approach to weight loss. ^[8]

Dietary Modification

Diets that focus on heart health play a crucial role in therapy for metabolic syndrome. Diets that are rich in vegetables, fruits, whole grains, lean protein sources, but low in refined carbohydrates, have less sugar, and low saturated/trans-fat. The goal for such dietary modifications is to make every calorie count by improving the quality of the calories consumed. The following are various dietary approaches used for this purpose: ^[7]

1. **Mediterranean Diet:** In this diet, red meat and sweets are kept to a minimal quantity and more emphasis is given to vegetables, legumes, nuts, fish, olive oil, and whole grains. This inherently increases the amount of high fiber and healthy fats. High fiber reduces the occurrence of sugar spikes and triglycerides. Adherence to this diet has shown reduced risk of metabolic syndrome and cardiovascular diseases, and improvement in cholesterol profile and insulin sensitivity is seen.
2. **DASH Diet:** DASH diet stands for Dietary Approaches to Stop Hypertension. This diet focuses on reducing the amount of sodium intake. Focus is given on fruits, vegetables, and low-fat dairy. This diet was originally developed for reducing hypertension by decreasing sodium intake and increasing potassium intake, but has also shown high potential in decreasing weight and improving lipid and glucose levels.
3. **Lower Carbohydrate or Low Glycemic-Index Diets:** One of the best methods to reduce blood sugar and triglyceride levels is moderating refined carbohydrate levels. The calorie goal is maintained by replacing some carbohydrates with protein and healthy fats, which improves the glycemic index and also promotes satiety.
4. **Overall Caloric Reduction:** Overweight patients benefit from a calorie deficit, so it is important that whichever diet is chosen maintains a calorie deficit for the patient. Instead of opting for smaller, more aggressive fad regimens, patients benefit from long-term term balanced portion-controlled diets. Simple measures like eliminating sugar, reducing portion size, and minimizing fast food work for many.

Simple measures like prepping food at home, reading food labels, and following sample meal plans can make a great difference in weight management. Clinicians can offer dietary counseling or refer patients to registered nutritionists. Patients can benefit from meal replacements and other structured programs like diet tracking apps. Any meal plan that is sustainable in terms of satiety, cultural appropriateness, and is enjoyable can be adhered to by the patient for a long term and provide lasting benefit. Regular follow-ups should be done to track the changes and keep patients motivated. ^[10]

Physical Activity

Individuals with metabolic syndrome benefit greatly from regular physical activity. Exercising daily has shown positive changes in insulin sensitivity, helps in weight reduction, lowers blood pressure, and raises HDL cholesterol. According to the American Heart Association, a moderate intensity workout like brisk walking for 150 minutes or vigorous activity for 75 minutes is suggested to improve cardiovascular health. A daily workout of moderate intensity for 30 minutes with some resistance training 2-3 times a week helps in building muscle mass, which increases basal metabolic rate and hence helps patients with metabolic syndrome. Small changes in lifestyle, like taking stairs instead of elevators, walking while taking calls, and doing active household work, contribute to overall energy expenditure. ^[7,8]

A sedentary lifestyle should be avoided at all costs by implementing small changes like 10-minute walks, which can be incrementally increased with time and enduring capacity. Quantifying the patient's progress by encouraging step goals (8000-10000/day). Exercising regularly reduces the waist circumference even in the absence of significant weight loss. A combination of diet and exercise has shown the best results, and higher syndrome resolution is seen in these combination treatment modalities. ^[9]

Additional Lifestyle Measures

Several other lifestyle interventions are important in managing metabolic syndrome:

Smoking Cessation: Smoking has been shown to increase insulin resistance and inflammation, compounding cardiovascular risk. Smoking cessation regimens should be given to patients that include nicotine replacement and support to quit tobacco. **Alcohol in Moderation:** Alcohol intake has been shown to increase triglyceride levels, and complete abstinence should be advised in patients with increased levels of triglycerides. 1 drink per day for women and 2 for men has been advised for patients to decrease blood pressure.

Sleep and Stress Management: Patients with a history of poor sleep have also shown increased predisposition towards metabolic syndrome. Poor sleep can be a result of both decreased sleep duration and poor sleep quality because of obstructive sleep apnea. Patients who have a history of bruxism or snoring should be screened for sleep apnea, and treatments like CPAP should be suggested for such patients. Poor sleep as a result of stress should also be considered, and such cases should be managed with yoga, relaxation, and mindfulness. These measures have been shown to decrease insulin resistance and improve metabolic health.

Metabolic syndrome is one of the few chronic conditions that can be completely modified by lifestyle changes like weight loss and fitness gains. A rise in HDL and a fall in triglycerides is seen within a few weeks of exercising. Improved diet and exercise have shown a drop in blood pressure and weight loss. Decreased sodium intake in the diet has shown a remarkable drop in blood pressure. This reversal translates to reduced long-term risk of heart disease and diabetes. Conveying this hopeful message can motivate patients to adhere to the sometimes-challenging lifestyle modifications. ^[11]

Role of Pharmacotherapy and Comprehensive Risk Factor Control

Sometimes the individual risk factors require medical management since they are above threshold level for a long time. All risk factors should be optimized during treatment of metabolic syndrome. For instance, if after lifestyle efforts, a patient's LDL cholesterol or blood pressure is still above goal, starting a statin or antihypertensive is indicated following guideline-directed therapy for dyslipidemia or hypertension. ^[12] **Management of Dyslipidemia:** Statin therapy should be initiated in patients with elevated atherogenic cholesterol. This reduces LDL and non-HDL cholesterol. Statins also tend to lower triglycerides and raise HDL. For severe hypertriglyceridemia (>500 mg/dL), fibrate therapy or high-dose omega-3 fish oil may be used to reduce pancreatitis risk, but treating the underlying insulin resistance with lifestyle (and possibly metformin) is fundamental.

Blood Pressure Control: A target blood pressure of <130/80 mmHg should be maintained in patients with metabolic syndrome. Standard protocols for hypertension management include ACE inhibitors, ARBs, calcium channel blockers, and diuretics. Coexisting conditions should also be considered while choosing the drug; for instance, patients with metabolic syndrome and prediabetes benefit greatly from ACE inhibitors. Regular at-home monitoring of blood pressure helps in guiding the management therapy. ^[13]

Glycemic Management: Prediabetic patients mainly benefit from lifestyle changes. Some studies suggest starting metformin in prediabetic patients, which helps in stopping the progression from pre diabetes to diabetes. Patients with type 2 diabetes are often started on medications like SGLT2inhibitors and GLP-agonists. These medicines have shown a reduced risk of cardiovascular events. ^[14] **Antithrombotic and Other Measures:** Aspirin therapy should be started in patients with metabolic syndrome who have high cardiovascular risk. Such patients should first be evaluated for bleeding risk, and if the risk is less than the benefit of aspirin therapy, it should be started.

Timely vaccinations for diseases like influenza and hepatitis B should be advised for patients with metabolic syndrome, as they may trigger cardiovascular events in severe cases. ^[14] When the individual components of metabolic syndrome are treated to goal, the overall outcome shows more improvement even if the whole

syndrome is not cured. According to certain clinical trials, it is seen that when individual elements of the syndrome are targeted instead of trying to cure the whole syndrome at once, better results are seen. Another advantage of recognizing metabolic syndrome is that other abnormalities that would have generally been missed are also diagnosed, and prompt treatment can be given. For instance, if a patient with hypertension is being treated for metabolic syndrome, then he will also be screened for diabetes and dyslipidemia, which might have been missed otherwise. ^[14] Patient education is of utmost importance in the management of metabolic syndrome. Patients should be motivated by giving them goals and targets, and when they see the difference lifestyle changes can make without taking medications, motivation for the same is imbued, and patients are encouraged to make healthy lifestyle changes. ^[14]

Conclusion

Clustering of various modifiable risk factors, which, when presented together, pose a serious threat to health, is termed metabolic syndrome. Metabolic syndrome is screened by setting certain guidelines for obesity, blood pressure, and other risk factors, and adhering to the standard target ranges. Lifestyle modification is the mainstay for the management of metabolic syndrome. Treating the risk factors individually by modifying lifestyle plays an important role in the management of metabolic syndrome. All the risk factors should be treated simultaneously. Lifestyle modification has proven to reverse metabolic syndrome if implemented on time. A multidisciplinary, team-based care model involving dietitians, exercise specialists, diabetes educators, and sometimes endocrinologists or cardiologists – can enhance support for the patient and improve adherence.

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Author contributions

The text was written by the original author, although each author made significant contributions through data collecting and literature searches. Each author approved the final text, participated in the manuscript's critical assessment, and assumed full responsibility for the work.

Conflict of Interest

Authors declare they don't have any conflict of interest.

Ethical Approval

Not Applicable

References

1. Swarup S, Ahmed I, Grigorova Y, & Zeltser R (2024). Metabolic syndrome. In StatPearls [Internet]. StatPearls Publishing.
2. Alberti KGMM, Zimmet P, & Shaw J (2006). Metabolic syndrome—a new worldwide definition. A consensus statement from the International Diabetes Federation. *Diabetic Medicine*, 23(5), 469–480.
3. Kassi E, Pervanidou P, Kaltsas G, & Chrousos G (2011). Metabolic syndrome: definitions and controversies. *BMC Medicine*, 9(1), 48.
4. Cleeman JI (2001). 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).
5. Gregg EW, & Moin T (2021). New USPSTF recommendations for screening for prediabetes and type 2 diabetes: an opportunity to create national momentum. *JAMA*, 326(8), 701–703.
6. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, & Wong JB (2020). Behavioral counseling interventions to promote a healthy diet and physical activity

- for cardiovascular disease prevention in adults with cardiovascular risk factors: US Preventive Services Task Force recommendation statement. *JAMA*, 324(20), 2069–2075.
7. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, & Yanovski SZ (2014). 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, 63(25 Part B), 2960–2984.
 8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, & Ziaieian B (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 74(10), e177–e232.
 9. Peterseim CM, Jabbour K, & Kamath Mulki A (2024). Metabolic syndrome: an updated review on diagnosis and treatment for primary care clinicians. *Journal of Primary Care & Community Health*, 15, 21501319241309168.
 10. Craddick SR, Elmer PJ, Obarzanek E, Vollmer WM, Svetkey LP, & Swain MC (2003). The DASH diet and blood pressure. *Current Atherosclerosis Reports*, 5(6), 484–491.
 11. Dopp JM, Reichmuth KJ, & Morgan BJ (2007). Obstructive sleep apnea and hypertension: mechanisms, evaluation, and management. *Current Hypertension Reports*, 9(6), 529–534.
 12. Arozal W, Louisa M, & Soetikno V (2020). Selected Indonesian medicinal plants for the management of metabolic syndrome: molecular basis and recent studies. *Frontiers in Cardiovascular Medicine*, 7, 82.
 13. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, & American Heart Association (2023). Cardiovascular–kidney–metabolic health: a presidential advisory from the American Heart Association. *Circulation*, 148(20), 1606–1635.
 14. Herman R, Kravos NA, Jensterle M, Janež A, & Dolžan V (2022). Metformin and insulin resistance: a review of the underlying mechanisms behind changes in GLUT4-mediated glucose transport. *International Journal of Molecular Sciences*, 23(3), 1264.