Bidirectional Relationship Between Metabolic Syndrome and Erectile Dysfunction

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Metabolic syndrome is highly correlated with erectile dysfunction (ED) according to direct and indirect evidence. The results of individual studies have shown that the frequency of ED in patients with metabolic syndrome varies between 26.7–76.2% among ethnic groups. ED occurs earlier and remains longer in patients with metabolic syndrome compared with those with organic ED without metabolic syndrome. The prevalence of ED increases and the International Index of Erectile Function score decreases as the number of abnormal metabolic items of metabolic syndrome increases. The pathogenesis of ED in patients with metabolic syndrome is likely multifactorial in nature, but endothelial dysfunction is the most important mechanism. Lifestyle modifications, including weight control may, be one of the best strategies for treating ED patients with metabolic syndrome. When treating an ED patient, physicians should determine the status of cardiac risks and metabolic syndrome to decrease heart diseases and promote the patient’s health.

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1. Introduction

Many studies have shown a correlation between atherosclerosis and erectile dysfunction (ED). One study considered that cardiovascular disease (CVD) may explain the etiology of ED in more than 50% of cases of ED. In different study populations, approximately 5–56% of ED patients reported CVDs. Furthermore, a high proportion (44–75%) of symptomatic cardiovascular patients have ED. Various risk factors of CVD, such as diabetes, hypertension, dyslipidemia, and smoking, have also been shown to have a close relationship with ED. Recently, metabolic syndrome (syndrome X, insulin-resistance syndrome) was identified as consisting of a constellation of metabolic abnormalities that confer increased risks of CVD and diabetes mellitus. The relationship of metabolic syndrome with CVD has been a hot topic, and data have also indicated a positive correlation between them. We address the question of “what is the relationship between metabolic syndrome and ED?” in this article.

2. Definition of Metabolic Syndrome

Metabolic syndrome has also been called the deadly quartet, syndrome X, and syndrome X plus. This implies that a person simultaneously has several abnormal metabolic factors, such as high blood sugar, high blood lipid, high blood pressure, a high body mass index (BMI), high waist circumference, and insulin resistance. However, definitions of metabolic syndrome are different among the different international groups. For example, insulin resistance is required for the definitions of the World Health Organization and European Group for the Study of Insulin Resistance, but it is not a required item in the definition of the National Cholesterol Education Program and Adult Treatment Panel III (NCEP ATP III). Additionally, the American College of Endocrinology proposed excluding obesity from the definition of metabolic syndrome because they thought obesity was a cause of insulin resistance, not an outcome. Diabetes has also been questioned by some experts because of its high...
cardiovascular risk compared with pre-diabetes and other risk factors.

While the current definitions of metabolic syndrome proposed by expert groups slightly differ, the definition of the NCEP ATP III seems to be more widely used in the literature because it is more helpful for investigators. Another definition proposed by the International Diabetes Federation (IDF) in 2005 is similar to that of the NCEP ATP III, and it has also attracted the attention of investigators and has been increasingly used in studies. The exact definitions of metabolic syndrome by the NCEP ATP III and IDF are given in Tables 1 and 2.

According to the definition of the NCEP ATP III, a case of metabolic syndrome is defined as having at least three abnormal items among waist circumference, triglyceride levels, high-density lipoprotein (HDL) cholesterol levels, blood pressure, and fasting glucose levels. The NCEP ATP III is slightly different compared with the IDF definition. Waist circumference beyond the cutoff point is required for a person to have metabolic syndrome according to the IDF definition. If a person has an abnormal waist circumference (central obesity) plus any other two abnormal items that person is regarded as having metabolic syndrome. In Taiwan, the Bureau of Health Promotion also proposed a local definition of metabolic syndrome for Taiwanese. The revised version released in 2006 is similar to the modified NCEP definition but waist circumference cutoff points were changed to ≥90 cm for men and ≥80 cm for women.

### 3. The Relationship Between Metabolic Syndrome and ED

All of the components of metabolic syndrome are common risk factors for CVD. Therefore, it is reasonable to propose that metabolic syndrome may be related to ED, and this suggests that endothelial dysfunction is an important mechanism responsible for metabolic syndrome causing ED.

There are some data showing risk factors related to ED. Diabetic patients have more frequent and more severe ED compared with patients with other cardiovascular risk factors. The quality of life of diabetic ED patients is lower than that of non-diabetic ED patients. Walczak et al. found that self-reported ED patients had a high prevalence of obesity. Another study by Bacon et al. showed that people with a BMI of >28.7 have a 30% greater risk of experiencing ED compared with those with a BMI of <25. With regard to hyperlipidemia, Wei et al. showed that the relative risk of ED for male patients with a total cholesterol >240 mg/dL was 1.83 compared with those with a total cholesterol <180 mg/dL. Conversely, the relative risk of ED for patients with a HDL

### Table 1 NCEP definition of metabolic syndrome

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Value of the cutoff point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>(waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥102 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥88 cm</td>
</tr>
<tr>
<td>Triglyceride level</td>
<td>≥150 mg/dL or under specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL or under specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL or under specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mmHg or under specific treatment for hypertension</td>
</tr>
<tr>
<td>Fasting glucose a</td>
<td>≥100 mg/dL or diabetic patient under treatment.</td>
</tr>
</tbody>
</table>

Metabolic syndrome is defined as having at least three abnormal items among waist circumference, triglyceride level, HDL cholesterol, blood pressure, and fasting glucose. *Fasting glucose when initially proposed in 2001 was defined as ≥110 mg/dL. NCEP = National Cholesterol Education Program; HDL = high-density lipoprotein cholesterol.

### Table 2 Metabolic syndrome for the Taiwanese by the new International Diabetes Federation (IDF) definition

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

Central obesity (defined as a waist circumference of ≥90 cm for Taiwanese men and ≥80 cm for Taiwanese women, with ethnicity specific values for other groups) plus any two of the following four factors:

1. Raised triglyceride levels: ≥150 mg/dL (1.7 mmol/L), or having specific treatment for this lipid abnormality
2. Reduced high-density lipoprotein cholesterol: <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females, or having specific treatment for this lipid abnormality
3. Raised BP: systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension
4. Raised FPG ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If >5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but it is not necessary to define the presence of the syndrome

*These values were updated from those originally presented to ensure consistency with the ATP III cutoff points. BP = blood pressure; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.
cholesterol of >60 mg/dL was 0.3 compared with patients with a HDL cholesterol of <30 mg/dL.15

Some cross-sectional studies have correlated metabolic syndrome with ED, but few prospective studies have investigated this issue. Grover et al. found that the odds ratio (OR) of having ED with metabolic syndrome was 1.45, and metabolic syndrome was an independent risk factor predicting ED.16 Gunduz et al. concluded that metabolic syndrome has a high correlation with ED.17 Demir showed that the International Index of Erectile Function (IIEF) score in patients with metabolic syndrome was significantly lower than those without metabolic syndrome, and the IIEF score decreased as the number of abnormal metabolic items increased.18 Therefore, they suggested that metabolic syndrome is a risk factor for ED. Esposito and colleagues noted a strong correlation between the prevalence of ED and the number of abnormal metabolic items.19

4. Physical Activity, Alcohol Consumption, and ED

Physical activity has been shown to have protective effects against CVD via the mechanism of improving glucose tolerance, lowering blood pressure, preventing obesity, and improving the lipid profile and endothelial function.20 Daily low-dose alcohol has also been shown to confer CVD protection by improving the HDL level, insulin sensitivity, and postprandial glucose level.21 Therefore, study results exploring the relationships of physical activity and alcohol consumption with ED can also be used as evidence for the correlation between metabolic syndrome and ED.

4.1. Physical activity and ED

Results from the Health Professionals Follow-up Study showed that weekly physical activity of 2.7–7.6, 7.7–16.5, 16.6–32.6, and >32.6 metabolic equivalents (METs) significantly decreased the risk of ED by 10%, 10%, 20%, and 30%, respectively, compared with physical activity of <2.7 METs per week. The authors suggested that physical activity was significantly inversely associated with erectile function.22 Prospective results from the Massachusetts Male Aging Study revealed that a daily energy consumption of >200 kcal may decrease the risk of ED by 29%, but this was not statistically significant.23 A meta-analysis study from Hong Kong summarized a cross-sectional study, two cohort studies, and one randomized clinical trial, and the results showed summary estimates for adjusted ORs of physical activity on ED of 0.53 (0.31–0.91), an OR of 0.63 (0.43–0.93) for moderate physical activity, and an OR of 0.42 (0.22–0.82) for high physical activity. The authors suggested that an apparent “protective” effect of physical activity on ED should be further investigated using large-scale cohort studies or randomized clinical trials.24

4.2. Alcohol consumption and ED

Results from both the Health Professionals Follow-up Study and Massachusetts Male Aging Study found that the effect of alcohol on ED was neutral.22,23 Another Finnish 5-year follow-up study also reached the same conclusion.25 A meta-analysis reviewed the results of one cross-sectional study and two cohort studies.26 The authors noted that there was a protective association of alcohol against ED in the cross-sectional study, but the two cohort studies demonstrated no significant findings. Therefore, they suggested that further research was required to confirm the effect of alcohol on ED development. Findings of a recently published study from Western Australia suggested a modest negative association between alcohol consumption and ED, and CVD and cigarette smoking confounded the association. On further adjustment for CVD and cigarette smoking, age-adjusted odds of ED were reduced by 25–30% among alcohol drinkers.27

5. Testosterone in Metabolic Syndrome and ED

The scientific evidence from cross-sectional and cohort studies supports an association between low testosterone/low sex hormone-binding globulin levels and metabolic syndrome.28 Some studies confirmed that testosterone treatment reduces waist circumference, a component of metabolic syndrome.29,30 Another study administering testosterone to restore levels to mid-normal values for a duration of 8–9 months found decreased visceral fat mass, fasting glucose, lipid levels, and diastolic blood pressure, and improved insulin sensitivity.31 All of the above evidence confirms the relationship between low testosterone and metabolic syndrome.

It is well known that hypogonadism in men usually results in loss of libido and potency, which can be restored by androgen administration, and testosterone affects libido and also exerts essential effects on the anatomical and physiological substrates of penile erection.28 Therefore, in addition to influencing libido and penile erection, metabolic syndrome may be another route through which hypogonadism affects ED.

6. Summary of the Current Status of Metabolic Syndrome and ED

6.1. Epidemiology

Metabolic syndrome is highly correlated with ED according to direct and indirect evidence from the current literature. The results of individual studies show that the frequency of ED at 26.7–76.2% in patients with metabolic syndrome varies among ethnic groups.17–19 ED occurs
earlier and remains longer in ED patients with metabolic syndrome compared with those with organic ED without metabolic syndrome.\textsuperscript{32} The prevalence of ED increases and the IIEF scores decrease as the number of abnormal metabolic items of metabolic syndrome increases.\textsuperscript{18,33} Age may influence the relationship between metabolic syndrome and ED. A study using the IDF definition found that metabolic syndrome in men older than 50 years was significantly associated with a higher proportion of moderate to severe ED, but not in men younger than 50 years.\textsuperscript{34}

6.2. Mechanism

6.2.1. The role of endothelial dysfunction

Endothelial dysfunction is suggested to be a mechanism through which metabolic syndrome causes ED. Esposito et al. found that the prevalence of ED and the number of abnormal metabolic items are strongly correlated, and they also showed that the index of endothelial dysfunction decreased by 6-fold and C reactive protein increased by more than 3-fold in patients with metabolic syndrome.\textsuperscript{19} A review paper published in 2007 also found inflammatory status related to endothelial dysfunction.\textsuperscript{35} After performing a comprehensive evaluation of the available published data in full-length papers that were identified in MedLine up to July 2007, the authors found associations among metabolic syndrome, ED, and an increased inflammatory state. They also suggested that increased circulating levels of inflammatory and endothelial-prothrombotic compounds are related to the presence and severity of ED. An age-matched case-control study showed that penile arterial 5-, 10-, and 20-min peak flow velocities in ED patients with metabolic syndrome were decreased compared with those of ED patients without metabolic syndrome.\textsuperscript{36} The authors concluded that metabolic syndrome appears to be a potential risk factor for ED which may exert its effect by decreased arterial inflow due to endothelial dysfunction.

6.2.2. Other proposed pathogenic routes

Endothelial dysfunction is not the only mechanism proposed for how metabolic syndrome affects ED. According to data from organic ED patients after a full evaluation, including laboratory and ultrasound assessments of endothelial function, Mazo et al. concluded that the pathogenesis of ED in patients with metabolic syndrome is multi-factorial in nature.\textsuperscript{37} They suggested that ED is primarily caused by arteriogenic disorders which are coupled with neuropathic disorders in almost half the patients and with hormonal factors in 1 of 3 patients. Apart from the above factors, they also considered that the psycho-emotional status is very important in the development of ED in patients with metabolic syndrome.

7. Benefits of Lifestyle Modification in Treating ED Patients with Metabolic Syndrome

A previous study on obese treatment revealed that body weight reduction can significantly increase IIEF scores and significantly improve the lipid profile, blood pressure, blood sugar, blood insulin, C-reactive protein, and interleukin levels.\textsuperscript{38} That study suggested that lifestyle modifications including weight control may be one of the best treatments for ED patients with metabolic syndrome.

Metabolic syndrome may affect the response to sildenafil treatment. A Japanese study using the IDF definition demonstrated a negative impact of metabolic syndrome on the responsiveness to sildenafil.\textsuperscript{39} They found that erectile function and the response rate to sildenafil decreased as the number of metabolic syndrome components increased. This implied that when treating ED patients with metabolic syndrome, in addition to prescribing phosphodiesterase type 5 inhibitors, the importance of lifestyle modifications should be recognized.

8. Future Suggestions for Defining Metabolic Syndrome

One study found that the NCEP definition of metabolic syndrome was better than the IDF definition in predicting hypogonadism and impaired penile blood flow.\textsuperscript{40} A joint interim statement for harmonizing recommendations for metabolic syndrome was published in October 2009.\textsuperscript{41} This article represents the outcome of a meeting between several major organizations in an attempt to unify criteria. It was agreed that there should not be an obligatory component (e.g., the NCEP definition). A single set of cutoff points should be used for all components except for waist circumference for which further work was required. In the interim, national or regional cutoff points for waist circumference should be used (e.g., the IDF definition). Additionally, Taiwanese can use the NCEP definition while the waist circumference cutoff points should be changed to $\geq 90$ cm for men and $\geq 80$ cm for women, similar to the 2006 revised form proposed by the Taiwan Bureau of Health Promotion.

9. Conclusions

There is a lot of evidence in the literature suggesting a relationship between metabolic syndrome and ED. Therefore, sexual health may be a portal to men’s health. When treating an ED patient, physicians should use a more comprehensive approach to explore the status of cardiac risks and metabolic syndrome to decrease heart disease and promote the patient’s health.
References


