



Metabolic Syndrome and Its Effect on Wound Healing

This common condition is often overlooked and certainly undertreated.

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Introduction

Wound care and limb salvage centers are frequently focused around patients with uncontrolled diabetes, neuropathy, venous insufficiency, and other conditions that pose complications to wound healing. However, patients with metabolic syndrome, or “MetS,” should also raise concern for foot and ankle surgeons performing wound care. Currently, the prevalence of adults in the United States with MetS is greater than that for diabetes and will only continue to rise with increasing rates of obesity and the aging population, both factors correlated with developing the syndrome.¹

A recent study by Moore and colleagues from the Centers for Disease Control and Prevention (CDC) found that more than one third of U.S. adults (defined as 18 years or older) meet the criteria for MetS.¹ In comparison, data from 2015 found that just over one tenth (12.2%) of U.S. adults are diagnosed with diabetes mellitus.² Not surprisingly, obesity, as defined as a body mass index (BMI) of greater than 30, has tripled worldwide since 1975, accelerating the number of diagnoses of MetS.³ The current article reviews the diagnosis of MetS, its prevalence,

and its effects on wound healing in the diabetic population.

What Is Metabolic Syndrome (MetS) and How Is It Diagnosed?

Metabolic syndrome was first

described as “Syndrome X” in 1988 by G.M. Reaven, who noted a constellation of symptoms such as insulin resistance, dyslipidemia, and high blood pressure that predisposed patients to cardiovascular disease (CVD).⁴

There are a variety of theories that exist to explain the pathophysiology of these symptoms and how these criteria were developed. One theory describes insulin resistance or intolerance perpetuating dyslipidemia and hypertension.⁵ A second theory points first to the increase in visceral over subcutaneous fat as the driver of insulin resistance and, therefore, the true precursor to dyslipidemia.⁶ Whatever the cause, insulin resistance appears to play a significant role in the pathophysiology.

In short, metabolic syndrome is a “dysmetabolic phenotype” that may depend on levels of adiposity, physical fitness, or individual genetics.⁵

The criteria for MetS was originally developed to identify those people at risk for cardiovascular disease and to aggressively treat the individual symptoms (Table 1). Technically, a diagnosis of MetS is made when three or more of the criteria are

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TABLE 1: Criteria for Metabolic Syndrome

*Three or more of the following:**

Fasting glucose > 110 mg/dL or Type 2 Diabetes Mellitus
Triglycerides > 150 mg/dL or on anti-lipidemic treatment
Decreased HDL levels < 40 mg/dL (men); < 50 mg/dL (women)
Blood pressure > 130/85 mmHg or history of hypertension
Abdominal obesity as defined by elevated waist circumference (based on country populations)

* While criteria have been proposed and revised by the World Health Organization (WHO), International Diabetes Federation (IDF) and other groups, a consensus was developed in 2005. The National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III and International Diabetes Federation (IDF) compromised on a definition and noted having metabolic syndrome as the presence of three or more of the above criteria.⁴



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present. However, it is advised that rather than focus on diagnosing patients with MetS, a medical provider should instead use the criteria as a tool to be aware of a patient's overall

healing, so might patients with metabolic syndrome.

Does Met-S Affect Wound Healing?

Wound healing is traditionally noted to include three stages: hemostasis, inflammation, repair and re-

tractant protein-1 (MCP-1), and matrix metalloprotease 9 (MMP-9) were found to be higher in the serum of patients who developed diabetic foot ulcers (DFUs) that failed to heal compared to levels of these markers in patients whose DFUs healed in a timely manner.¹² Similarly, inflammatory markers such as TNF-alpha and MCP-1 have been noted to be up-regulated in the serum of patients with MetS.^{13,14} Because similar pro-inflammatory environments exist in the skin of patients with MetS and patients with non-healing DFUs, it can be presumed that patients with MetS may present similar difficulties with wound healing.

A second similarity between the skin of patients with diabetes and patients with MetS is increased glycation of collagen. It has been shown histologically that abnormal deposition of elastin in the dermis, thickening of the basement membrane and T-cell lymphocytic infiltration around capillaries occur in the skin of uncontrolled diabetic patients and MetS patients.⁴ These alterations are a prominent feature of glycosylation of collagen and make for a less resilient and reparative environment. This is a

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risk for cardiovascular disease. For the wound care specialist or foot and ankle surgeon, the presence of these criteria may suggest difficulties with wound healing.

Is Met-S Associated with Diabetes?

Because MetS revolves around the complex pathophysiology of insulin resistance, the development of diabetes can be considered the “end-stage” of MetS. In fact, in an eight-year study, Wilson, et al. found that patients with MetS were four times more likely to develop Type 2 diabetes mellitus (T2DM) than those without MetS.⁷ However, it is important to point out that not all patients with diabetes have or have had metabolic syndrome.

A prospective study in the United Kingdom by Cull, et al. examined 5,102 patients with newly diagnosed T2DM and found a prevalence of 61% for MetS.⁸ Additionally, a study by Bruno, et al., noted a prevalence of 76% within a T2DM population. Additionally, they found no increased risk of cardiovascular events for those with MetS on top of T2DM.⁹ The study suggested that diagnosing patients with T2DM already with MetS as well added no clinical benefit to predicting cardiovascular risk.

While metabolic syndrome and diabetes may present similar metabolic disturbances, the physician should not make the assumption that a patient with diabetes automatically satisfies the criteria for metabolic syndrome and vice versa. However, just as patients with uncontrolled diabetes present concerns for wound

modeling. Progression to the repair and remodeling stage can be complicated by persistent pro-inflammatory environments in which wounds may enter a more chronic inflammatory stage. While an abundance of research regarding metabolic syndrome and wound healing does not exist, metabolic syndrome can present concerns for wound care specialists.

While the link between the metabolic abnormalities associated with MetS and skin conditions is not fully understood, chronic inflammatory skin conditions such as adult acne and psoriasis are highly correlated

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with developing insulin resistance and MetS.¹⁰ The skin of patients with MetS may show increased levels of inflammatory and oxidative stress markers which prevent timely remodeling. Additionally, skin of patients with MetS has been shown to have decreased levels of matrix metalloprotease inhibitors and increased levels of metalloproteases, leading to more collagen degradation and dysregulated repair.⁴ Increased levels of matrix metalloproteases are known contributors to delays in wound healing and a frequent inhabitant of biofilms on wound surfaces.¹¹

In a 2012 study by Dinh, et al., levels of inflammatory markers such as TNF-alpha, monocyte chemoat-

tractant protein-1 (MCP-1), and matrix metalloprotease 9 (MMP-9) were found to be higher in the serum of patients who developed diabetic foot ulcers (DFUs) that failed to heal compared to levels of these markers in patients whose DFUs healed in a timely manner.¹²

Similarly, inflammatory markers such as TNF-alpha and MCP-1 have been noted to be up-regulated in the serum of patients with MetS.^{13,14} Because similar pro-inflammatory environments exist in the skin of patients with MetS and patients with non-healing DFUs, it can be presumed that patients with MetS may present similar difficulties with wound healing.

Lastly, patients with metabolic syndrome also present surgical concerns. Menendez et al. examined 669,841 operative ankle fractures in patients with metabolic syndrome and without. Patients with metabolic syndrome experience a higher complication rate than patients without metabolic syndrome (2.3% vs. 0.3% respectively).¹⁵

How Do We Treat or Mitigate the Effects of MetS?

Patients with traumatic or surgical wounds who meet the criteria for MetS are a concern for the wound

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care specialist and foot and ankle surgeon. While no specific recommendations or change in treatment is recommended, vigilance and extreme caution is advised with these patients as a non-healing, chronic wound may develop.

Patient counselling regarding weight reduction and life-style changes are a critical part of the strategy for patients with MetS along with pharmacological interventions to control hyperlipidemia, hypertension, and diabetes. While pharmacological treatment is not a podiatric physician's primary role, counseling or referral to a nutritionist or personal trainer could help reduce the impact of MetS on a patient's overall health and improve one's propensity to heal. In fact, a systematic review from 2012 found that lifestyle modifications in the form of prescribed dietary changes and exercise regimens led to the resolution or reduction in severity of MetS criteria.⁶

Conclusion

Metabolic syndrome is a common medical condition that is often

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Awareness by the wound care specialist and foot and ankle surgeon and the detrimental effects of MetS on wound healing are critical to understand.

overlooked or certainly undertreated in patients with wounds or undergoing surgery. However, patients who fulfill the criteria for metabolic syndrome may present with skin conditions that may result in difficult-to-heal wounds and wound complications following surgery. These are not dissimilar to those encountered in patients with uncontrolled diabetes. Treatment is geared to controlling the underlying medical conditions, i.e. hyperlipidemia, hypertension, and diabetes. However, awareness by the wound care specialist and foot and ankle surgeon and the detrimental effects of MetS on wound healing are critical to understand. **PM**

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