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PERSPECTIVE

Guideline for the identification and management of cardiometabolic risk after spinal cord injury: a case of unsubstantiated recommendations

Michael D. Stillman[1] · Steve Williams[2]

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Abstract

The 2018 Guideline for the Identification and Management of Cardiometabolic Risk after Spinal Cord Injury (SCI) represented the first concerted effort to address a cluster of derangements and diseases that are claiming the lives of individuals living with injuries. Its contributors and authors scoured the literature, weighed the validity, importance, and clinical relevance of what data they found, and collaborated in an effort to meaningfully improve the health and lives of people with SCI. However, we are concerned that several of the guideline's central recommendations—particularly around screening for and detection of glycemic dysregulation and dyslipidemia—have been offered prematurely. In several instances, the authors cite data from studies of people without SCI and, in our opinion, inappropriately apply those findings to support their SCI-specific suggestions. In other instances, they recommend that we employ tests whose usefulness and clinical relevance have yet to be demonstrated among people living with injuries. In short, we fear that the authors have developed clinical guidelines that are inadequately supported by data. This guideline is an extraordinary show of collaboration, and is an important first step toward understanding and treating a number of secondary cardiometabolic effects of SCI. The lack of data underpinning several of its central recommendations—making them, in our opinion, unadoptable—underscores the inadequacy of research in this area and provides a roadmap for future investigative efforts.

Introduction

We accepted this "counterpoint" assignment with trepidation. While eager to help open dialogues about what is and is not known about cardiometabolic (CM) disease in spinal cord injury (SCI), we did not want to offend the guideline [1] authors. Many of them are colleagues and friends. We hold each of them in high regard.

These authors have taken on difficult work. Even while rightly attempting to improve and standardize the care of people with SCI, they emphasize the paucity of data addressing rates of diabetes, myocardial infarction, stroke, and death among those with injuries. This lack of "actionable" information informs our concerns about the guideline. We respect the authors' efforts, but feel that a number of their recommendations are insufficiently supported, hence, prematurely offered.

Glycemic dysregulation

The guideline suggest that clinicians screen adults with SCI for impaired glucose tolerance (IGT) and diabetes mellitus (DM) every 3 years, and that either fasting plasma glucose (FPG), glycohemoglobin (HbA1c), or oral glucose tolerance testing (OGTT) be used. As it has never been proven that incidence of DM increases with duration of injury, the screening interval was adopted from American Diabetes Association recommendations [2] that do not specifically address SCI.

Diabetes does seem to be prevalent among people with SCI, though the scope of the problem has not been well clarified. Early work from the Veterans Administration (VA) Hospital System suggests that between 13% and 51% of people living with SCI are diagnosed with DM when

✉ Michael D. Stillman
michael.stillman@jefferson.edu

[1] Internal Medicine and Rehabilitation Medicine, Sydney Kimmel Medical College of Thomas Jefferson University, 1100 Walnut Street, Suite 601, Philadelphia, PA 19107, USA

[2] Rehabilitation Medicine, Sydney Kimmel Medical College, Philadelphia, PA, USA

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undergoing OGTT [3, 4], yet in our own study of community-dwelling individuals with injuries [5], only 1 of 19 had a 2-h glucose level over 200 mg/dL. Our sense—though, admittedly, unsubstantiated—is that VA data from the 1980s and 1990s may no longer be applicable, particularly with the recent emphasis on participation in exercise programs and activity-based therapies for people with SCI.

Assuming, however, that people with SCI are at risk for IGT and DM, it is important to understand the utility of the three screening tests recommended in the guideline. It is known that there is no correlation between FPG and OGTT in the setting of SCI. In Duckworth et al. and Bauman et al. participants who were diagnosed with IGT and DM during OGTT had essentially normal FPG levels [4, 6], and it is believed that the glucose excursions observed during those test were due to the loss of skeletal muscle ("sarcopenia") that ordinarily serves as a reservoir for glucose storage. People with SCI may have glucose "spikes" after mealtime in the setting of background euglycemia, hence, may "fail" OGTT while maintaining unconcerning FPG levels.

Complicating this problem is an apparent lack of correlation between HbA1c and OGTT results in people with SCI. In our own work [5], 9 of 19 individuals with SCI had an elevated HbA1c or 2-h glucose level, *but only two had both* (Table 1). One participant had an HbA1c of 5.9%, diagnostic of IGT, but a 2-h glucose of 210 mg/dL, indicative of DM. The other had an HbA1c of 6.1% and a 2-h glucose of 170 mg/dL—both consistent with IGT. Unpublished data from a study extension show that among 32 participants with SCI, 6 have elevated HbA1c levels, 11 have 2-h glucose levels ≥140 mg/dL (indicating IGT or DM), but only two have both.

The literature comparing HbA1c with 2-h glucose levels for detection of DM is admittedly confusing. While there seem to be reliable cut-off values for both at which risk of retinopathy increases [7], several authors have shown poor correlation between the tests in specific patient populations.

Table 1 Comparison of HbA1c and OGTT among people with SCI

Subject	HbA1c	2 h OGTT Glucose
1	5.3	183
2	6.0	89
4	5.3	182
5	6.1	92
6	5.1	144
12	5.8	119
14	5.9	210
16	6.1	170
17	5.9	97

HbA1c 5.7–6.4 indicates IGT; ≥6.5 indicates DM. 2 h OGTT 140–199 indicates IGT; ≥200 indicates DM. Data from Stillman et al. [5]

In Hjellestad et al's study of people with vascular disease [8], HbA1c was only 45% sensitive in detecting DM when compared with OGTT. Picon et al. studied women previously diagnosed with gestational diabetes and found HbA1c to be only 23% sensitive [9] in diagnosing DM. Due to the unique physiology of SCI, HbA1c and OGTT may offer completely different impressions of our patients' ability to metabolize glucose. The HbA1c captures an individual's degree of glucose exposure over time, rather than reflecting the episodic excursions reflected by OGTT [7]. As people with SCI tend to have postprandial hyperglycemia but fasting euglycemia, their 2-h glucose levels may be elevated even if their HbA1c results are normal.

Given the lack of correlation between FPG, HbA1c, and OGTT among people with SCI, these three tests cannot be considered equally valid for the detection of IGT and DM in the setting of injury. As HbA1c reflects one's "overall" ability to metabolize glucose, we feel that this test is most useful to our patients. However, we suggest that prior to adopting the current guideline, we set ourselves to answer the following questions:

(1) Are postprandial glucose "spikes" seen in some people with SCI *clinically* significant? That is, are intermittent glucose excursions associated with microvascular consequences?
(2) Which of the three proposed screening tests best correlates with vascular complications of IGT and DM?

Dyslipidemia

The guideline suggests screening asymptomatic adults with SCI for dyslipidemia at least every three years, with more frequent testing for those with multiple cardiovascular (CV) risk factors. This recommendation is based on American Association of Clinical Endocrinologists guidelines [10] that offer individualized screening intervals for a number of patient populations but do not address special considerations in SCI.

Dyslipidemia in SCI has been well described. The primary and most common derangement is low high-density lipoprotein (HDL) levels [11], but LaFountain et al. have drawn attention to triglycerides (TG), as "adverse" values may be lower in people with SCI than in those without [12]. Despite having "benign" appearing lipid profiles, people with SCI seem to be at risk for accelerated atherosclerosis and coronary artery calcification. Both Bauman et al. and Lee et al. found high rates of positive stress tests among asymptomatic people with SCI [13, 14], and Orkazai et al. described higher coronary artery calcium scores among people with SCI than among matched non-injured controls [15].

Despite the fact that CV disease causes between 18.4% and 25% of deaths among people with SCI [16–18], *no studies are available to help guide our clinical practice or our risk-reduction efforts*. Nash et al. found that Niacin therapy improves the lipid profiles of people with SCI but did not follow other clinical outcomes [19]. Stillman et al's retrospective study found a 21% reduction in mortality among veterans with SCI who had been treated with HMG-CoA reductase inhibitors ("statins") [20], but the work was limited by its small sample size, the homogeneity of its subjects, and the fact that it has yet to be replicated.

Contending with the difficult topic of dyslipidemia in SCI, the guideline authors suggest consideration of statin therapy with goals of reducing TG levels to <150 mg/dL and increasing HDL levels to over 40 mg/dL in men and 50 mg/dL in women. In doing so, they cite two trials from the cardiology literature, one of which is unconvincing and one of which offers results that are not easily applicable to people with SCI.

HOPE-3 was a placebo-controlled trial investigating statin use in people with risk factors for CV disease but without elevated low-density lipoprotein (LDL) levels [21]. With just over 5 years of follow up, statin therapy yielded a 1.1% absolute risk reduction (ARR) in the combined end-point of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke. However, the number of participants needed to treat to prevent any one of these co-primary outcomes was 91, and among subjects taking statins, there was no reduction in overall mortality, CV-related mortality, resuscitated cardiac arrest, or angina with evidence of ischemia. These results seem far less convincing than those from foundational cardiology studies that showed up to an ARR of 3.1% (25% relative risk reduction) in major adverse coronary events (MACE) among people with known CV disease or DM taking statins [22].

In the Jupiter Trial, people with normal LDL but elevated C-reactive protein (CRP) levels were assigned to take either rosuvastatin or placebo [23]. The study was stopped after <2 years, as those in the active treatment group had significant reductions in a number of outcomes including myocardial infarction, stroke, and unstable angina. While it is tempting to apply these findings to people with SCI—particularly as they tend to have higher CRP levels than do matched non-injured controls [24]—CRP may be affected by a number of factors including level of injury, decreased mobility, urinary catheter use, and recent infection [25–27]. There is simply no way to tease out whether an elevated CRP value in someone with SCI is due to endovascular inflammation or to the injury, itself.

Given the persistent uncertainty over which screening tests and pharmacological interventions may help reduce CV morbidity and mortality among people with SCI, the following questions ought to be answered prior to adoption of this guideline:

(1) Is Stillman et al's study of veterans with SCI reproducible? That is, can we demonstrate in a larger and more diverse subject pool—even retrospectively—that statin therapy significantly reduces mortality among people with SCI?
(2) Are there widely available and affordable tests that can predict large vessel atherosclerotic disease in SCI? Endothelial dysfunction (EDx) is found in people without SCI in the earliest stages of coronary artery disease (CAD) [28] and has been shown to predict MACE [29–31]. Are there inflammatory markers or office or laboratory-based tests for EDx that can reliably predict CAD and MACE among people with SCI and, hence, help direct preventive therapy to those most at risk?
(3) Does autonomic dysfunction—particularly autonomic dysreflexia—cause MACE among people with SCI? If so, what are we to do about that?

Conclusion

The guideline authors took on a worthy and ambitious project. In their introduction, they shared with readers which questions they had set out to address, and many of them focused on understanding the incidence of CV complications of SCI, clarifying which screening tests for CM disease are most accurate among people with SCI, and which interventions improve health outcomes. The fact that the Guideline failed to answer most of these questions speaks to an alarming paucity of evidence rather than lack of effort or vision by the authors. We feel that this Guideline was prematurely published and that some of its recommendations ought not to be adopted by clinicians caring for people with SCI. However, we feel with equal conviction that its authors have done a great service to our professional community and to individuals with SCI. In publicly grappling with what is and is not known about CM disease in SCI, they have both laid out an ambitious research agenda and challenged us all to do better. And, in this way, the document is invaluable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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