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ORIGINAL ARTICLE

International spinal cord injury endocrine and metabolic extended data set

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Objective: The objective of this study was to develop the International Spinal Cord Injury (SCI) Endocrine and Metabolic Extended Data Set (ISCIEMEDS) within the framework of the International SCI Data Sets that would facilitate consistent collection and reporting of endocrine and metabolic findings in the SCI population.

Setting: This study was conducted in an international setting.

Methods: The ISCIEMEDS was developed by a working group. The initial ISCIEMEDS was revised based on suggestions from members of the International SCI Data Sets Committee, the International Spinal Cord Society (ISCoS) Executive and Scientific Committees, American Spinal Injury Association (ASIA) Board, other interested organizations, societies and individual reviewers. The data set was posted for two months on ISCoS and ASIA websites for comments. Variable names were standardized, and a suggested database structure for the ISCIEMEDS was provided by the Common Data Elements (CDEs) project at the National Institute on Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH), and are available at https://commondataelements.ninds.nih.gov/SCI.aspx#tab=Data_Standards.

Results: The final ISCIEMEDS contains questions on the endocrine and metabolic conditions related to SCI. Because the information may be collected at any time, the date of data collection is important to determine the time after SCI. ISCIEMEDS includes information on carbohydrate metabolism (6 variables), calcium and bone metabolism (12 variables), thyroid function (9 variables), adrenal function (2 variables), gonadal function (7 variables), pituitary function (6 variables), sympathetic nervous system function (1 variable) and renin–aldosterone axis function (2 variables).

Conclusion: The complete instructions for data collection and the data sheet itself are freely available on the website of ISCoS (http://www.iscos.org.uk/international-sci-data-sets).

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INTRODUCTION

The purpose of the International Spinal Cord Injury (SCI) Endocrine and Metabolic Extended Data Set (ISCIEMEDS) is to standardize the collection and reporting of information on endocrine and metabolic function in accordance with the purpose and vision of the International SCI Data Sets.[1]

The majority of persons with SCI develop one or more endocrine and/or metabolic disorders.[2–14] Onset, diagnosis and treatment of these endocrine and metabolic disorders may affect the quality of life and longevity of persons with SCI. Head trauma associated with acute SCI may result in selective or global pituitary–hypothalamic insufficiency;[4,11,14–18] bilateral abdominal trauma may be associated with adrenal insufficiency.[19] Immobilization is generally associated with rapid and progressive bone mineral loss, often resulting in marked osteoporosis of the skeleton below the level of lesion.[5,7,20–26] With acute injury, there is atrophy of paralyzed muscle and the occurrence of absolute or relative adiposity.[27–30] Because of inactivity and adverse body compositional changes, individuals may develop abnormalities in carbohydrate and lipid metabolism that predispose to cardiovascular atherogenesis.[2,31–35] Abnormalities of the gonads (for example, acute and chronic testicular dysfunction in males and acute ovarian dysfunction in females) have been reported to occur.[3,8,12,13] Having SCI does not protect against having other fairly prevalent endocrine abnormalities, such as autoimmune thyroid dysfunction, especially in women, which may be precipitated by an acute stressful event, or traumatic events distant to the acute injury.[36] Hypotension with upright posture occurs frequently in persons with higher cord lesions because of a deficient or absent peripheral release of norepinephrine to vascular challenge with secondary reliance on the renin-angiotensin-aldosterone system to maintain vascular integrity.[9,10,37–39] When these disorders are clinically suspected, specific components of this data set may be used to assist in diagnosis and treatment.

The information collected in this ISCIEMEDS will generally be used in connection with data in the International SCI Core Data Set,[40] which includes information on date of birth and injury, gender, the cause of spinal cord lesion and neurologic status. It should be used together with International SCI Endocrine and Metabolic Basic Data

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Table 1 Outline of the development of the International SCI Endocrine and Metabolic Extended Data Set (ISCIEMEDS)

Steps	
1	The working group of the ISCIEMEDS prepared the first version of the ISCIEMEDS and a set of instructions (syllabus) via e-mail discussions.
2	The ISCIEMEDS was reviewed by members of the International SCI Data Sets Committee. The suggestions from the Committee members were discussed in the working group and appropriate changes were made.
3	The ISCIEMEDS was reviewed by Members of the International Spinal Cord Society (ISCoS) Executive and Scientific Committees and American Spinal Injury Society (ASIA) Board. The comments from the Committees/Board members were discussed in the working group and further adjustments were made.
4	Organizations and Societies and individuals with an interest in SCI-related endocrine and metabolic issues were also invited to review and comment on the ISCIEMEDS. The Data Set was also posted on the ISCoS and ASIA websites for two months to allow additional comments and suggestions. The suggestions provided were discussed by the working group and adjustments were made.
5	To finalize the ISCIEMEDS, members of the ISCoS Executive and Scientific Committees, and ASIA Board, review the data set for final approval.

Set,[41,42] because this data set includes the more basic information related to the endocrine and metabolic function in persons with SCI. In addition, it may be used together with other relevant International SCI Data Sets, when appropriate and relevant. As an example, fragility fractures in SCI are described in the International SCI Musculoskeletal Basic Data Set,[43] and therefore this item was not included in the present data set when collecting other variables related to osteoporosis of immobilization.

The diagnosis of endocrine and metabolic disorders has been clearly established in the general population. The direct application of this knowledge to persons with SCI can be accomplished by standard examination and laboratory determinations. The aim of this ISCIEMEDS is to present a standardized format for the collection and reporting of information on endocrine and metabolic functions and disorders, which have been identified in clinical practice and, after being collected, for possible research purposes. It is necessary in a particular patient to collect all variables provided in this data set; however, when a specific clinical issue, for example, hyperthyroidism, is being assessed, it is recommended that all variables that are related to thyroid function be collected. To permit valid comparison of information obtained, it is crucial that data be collected in a uniform manner. For this reason, each variable and each response category within each variable has specifically been defined in a way that is designed to promote the collection and reporting of comparable data. The use of a standard format is essential for combining data from multiple investigators and locations. Various formats and coding schemes may be equally effective and could be used in individual studies or by agreement of the collaborating investigators. The ISCIEMEDS will make it possible to evaluate and compare results from various published studies on endocrine and metabolic function after SCI, as an objective of the International SCI Data Sets.

The etiology of a SCI may be traumatic or nontraumatic. All lesions to the spinal cord, conus medullaris and cauda equina are included in the present context.

This document was produced under the auspices of the International Spinal Cord Society (ISCoS) and the American Spinal Injury Association (ASIA).

MATERIALS AND METHODS

The members of the ISCIEMEDS working group have extensive experience in both the clinical management and clinical research of endocrine and metabolic challenges associated with SCI.

The recommendations provided are based on their relevance to persons with SCI and the existence of published findings that support the validity of the measures selected in samples of persons with SCI. In order to ensure consistency in the data collection and to facilitate interpretation, detailed information is provided in a syllabus for each specific variable.

The development process of the ISCIEMEDS followed the steps outlined in Table 1.

When the ISCIEMEDS was finally approved, the Common Data Elements (CDEs) project at the National Institute on Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH) gave each variable a standardized variable name and the ISCIEMEDS had a suggested database structure. These are together with the complete syllabus for the ISCIEMEDS available at ISCoS (http://www.iscos.org.uk/international-sci-data-sets) and NIH, NINDS and CDEs project websites (https://commondataelements.ninds.nih.gov/SCI.aspx#tab=Data_Standards).

COMMENTARY ON THE DATA TO BE COLLECTED

The data sheet is included in the Appendix and available on the website of ISCoS (http://www.iscos.org.uk/international-sci-data-sets).

Listed below are the variables included in the ISCIEMEDS:

Date of data collection

Because the collection of data on endocrine and metabolic conditions may be performed at any time following the SCI, the date of data collection is imperative for computing the time that has lapsed after the initial SCI. This will permit the information obtained to be related to other data collected on the same individual at various time points.

Carbohydrate metabolism

Fasting glucose concentration. This variable will assess the ability to maintain fasting glucose homeostasis.

Classifications: Diabetes mellitus is diagnosed as a fasting glucose value $\geqslant 7\ \mathrm{mmol\,l^{-1}}$ ($126\ \mathrm{mg\,dl^{-1}}$); impaired glucose tolerance is defined as a fasting glucose value of $5.6–6.9\ \mathrm{mmol\,l^{-1}}$ ($100–125\ \mathrm{mg\,dl^{-1}}$).[44,45] An elevated fasting plasma glucose concentration would permit diagnosis of a disorder of oral carbohydrate tolerance. There is an increased prevalence of abnormalities in carbohydrate tolerance in persons with chronic SCI.[27,31]

Oral carbohydrate tolerance—2- h plasma glucose. This variable will assess the ability to handle an oral glucose load. Disorders of oral carbohydrate tolerance have been reported to be increased in persons with chronic SCI.[27,31] Because disorders of oral carbohydrate tolerance often will remain occult unless provocative testing is performed, and because those with SCI have an increased prevalence of impaired glucose tolerance and diabetes mellitus, it is recommended that practitioners perform oral glucose tolerance testing at least once every 5–10 years, or if there is suspicion of deterioration in carbohydrate tolerance.[44,45]

Oral glucose tolerance test—diagnostic classification. This variable will assess the ability to handle an oral glucose load.

Classifications: Diabetes mellitus is diagnosed as a stimulated value (2 -h plasma glucose) $\geqslant 11.1\ \mathrm{mmol\,l^{-1}}$ ($200\ \mathrm{mg\,dl^{-1}}$); impaired

glucose tolerance is defined as a stimulated value (2 -h plasma glucose) of 7.8–10.9 mmol l^{-1} (140–199 mg dl^{-1}).[44,45] Impaired glucose tolerance and type 2 diabetes mellitus are increased in persons with chronic SCI.[27,31] Any disorder associated with hyperglycemia would be expected to increase the risk of cardiovascular disease. Diabetes mellitus is a cardiovascular risk equivalent in stratifying risk for appropriate therapeutic intervention.[46,47]

Fasting plasma insulin. This variable will assess basal insulin reserve and peripheral insulin sensitivity.

Normal range: The normal range for fasting plasma insulin is 35–105 pmol l^{-1}. As a consequence of inactivity and adverse body compositional changes, persons with SCI have been found to be insulin resistant. The fasting plasma insulin level has been found to correlate with peripheral insulin sensitivity.[48]

Oral carbohydrate tolerance—2 -h plasma insulin. This variable will assess insulin reserve and peripheral insulin sensitivity.

Normal range: Stimulated <1076 pmol l^{-1}. Determinants of insulin resistance are strongly present in persons with SCI—decreased activity, decreased muscle mass and increased absolute or relative adiposity. A strong correlation exists between the insulin response to an oral glucose load and peripheral insulin sensitivity/resistance.[48]

Hemoglobin A1c (HgA_1c). This variable documents average glycemic control.

Normal value: $<6.5\%$. The integrated plasma glucose as reflected in the HgA1c value provides valuable information as to average carbohydrate handling.

Calcium and bone metabolism

Plasma/serum calcium concentration. This variable documents abnormality in circulating total calcium level.

Normal range: 2.2–2.6 mmol l^{-1}. Hypercalcemia during acute SCI may occur in individuals who have renal insufficiency (for example, dehydration, acute or chronic renal disease) and/or high bone turnover rates (for example, children, multiple bone fractures, Paget's disease or other conditions),[23,49] but hypercalcemia may also infrequently occur in adults with SCI without any predisposing conditions. Osteoporosis may result from paralysis and immobilization, but the skeletal loss may be made worse by a concomitant occult disorder in calcium metabolism. If the calcium concentration is elevated in an adult without a known pre-existing condition, it would suggest that another abnormality in calcium metabolism is present that may make the bone loss after SCI more pronounced. A high calcium concentration may suggest hyperparathyroidism and parathyroid hormone-independent conditions (for example, malignancy, vitamin D intoxication, granulomatous diseases, thiazides and so on), whereas a low calcium value may suggest poor dietary intake of calcium and/or vitamin D deficiency.

Plasma-ionized calcium concentration. This variable documents abnormality in circulating ionized calcium level.

Normal range: 1.1–1.4 mmol l^{-1}. The free cation concentration in plasma is referred to as 'ionized calcium.' Calcium is present in the blood in protein-bound and free forms, which together comprise the total plasma calcium concentration. The total plasma calcium concentration may vary dependent predominantly on the serum albumin concentration. Because the serum albumin concentration may vary because of acute or chronic illness, the plasma-ionized calcium concentration provides a direct determination of the bioactive plasma calcium concentration.[50] When there is uncertainty in the biologically active calcium concentration, often because of derangements in protein binding, it is recommended to perform a plasma ionized calcium concentration.

24-h Urinary calcium excretion. This variable documents renal excretion of calcium.

Normal range: <7.3 mmol kg^{-1} body weight. When the level of the plasma free calcium concentration is elevated or depressed, performing a 24-h urinary calcium excretion will assist to clarify the clinical picture, and also provide information on the magnitude of the disorder. For example, shortly after SCI, there is an increase in bone resorption, which elevates the plasma ionized calcium concentration. This will result in increased renal excretion of calcium, with the magnitude of calcium excretion directly related to the degree of bone resorption. Hypercalciuria may be associated with renal lithiasis.[22–25]

Spot urine calcium to creatinine ratio (Ca/Cr). This variable documents renal excretion of calcium.

Normal range: <0.057 mmol μmol^{-1} l^{-1}. In certain populations, such as children, a spot urine Ca/Cr is often more practical to obtain than a 24-h urine collection for calcium measurement. To exclude absorptive hypercalcemia, it is recommended that the spot urine Ca/Cr be performed after an oral calcium load. Although a linear correlation has been reported between a fasting first-morning spot urine Ca/Cr and 24-h urine collection for calcium measurement,[51] other reports have suggested a weak correlation between fasting or nonfasting spot urine Ca/Cr collection and 24-h urine collection for calcium measurement.[52,53] As such, a 24-h urinary calcium excretion is the preferred test to more definitively establish the diagnosis of hypercalciuria.

Serum vitamin 25-hydroxyvitamin D level. This variable documents low or normal body stores of vitamin D.

Normal range: 50–150 nmol l^{-1}. Persons with SCI have been identified to have a greater prevalence of being vitamin D deficient.[5] Measuring the level of 25-hydroxyvitamin D (25-OH D), the storage form of vitamin D, is accepted as the routine manner to exclude a vitamin-D-deficient state. A deficiency of vitamin D would reduce gut absorption of calcium and predispose to osteoporosis. Adequate intake and circulating levels of vitamin D are important to maintain skeletal integrity.[5,54] There exists controversy as to the acceptable lower limit of vitamin D concentration. The Thirteenth Workshop Consensus for vitamin D Nutritional Guidelines[55] and the Institute of Medicine[56] recommended a serum 25-OH D concentration of $\geqslant 50$ nmol l^{-1}. This value for 25-OH D was chosen for the general population primarily because of a lack of solid evidence provided by prospective controlled clinical trials to support the benefits of the higher threshold value, and because of potential adverse effects of higher 25-OH D values. The prior recommendations being appreciated, the Endocrine Society recommended a slightly higher lower limit of normal for serum 25-OH D concentration of $\geqslant 75$ nmol l^{-1} [57] because of the patient subpopulation referred to endocrinologists for care, considerations based on calcium metabolism[58–60] and variation in 25-OH D assay standardization and reproducibility. Because persons with SCI have severe sublesional osteoporosis, often have reduced calcium intake and have a tendency for low 25-OH D levels for a variety of reasons,[5] setting the lower limit for 25-OH D at $\geqslant 75$ nmol l^{-1} in this population seems reasonable.

Plasma parathyroid hormone level. This variable documents the level of parathyroid gland function.

Normal range: 10–65 ng l^{-1}. Elevation in the plasma parathyroid hormone (PTH) often causes excessive bone loss. If plasma PTH is elevated, it may worsen the bone loss associated with SCI. Secondary hyperparathyroidism may occur in persons with SCI because of insufficient or deficient levels of vitamin D.[5]

Plasma/serum N-telopeptide (NTX) concentration. This variable documents the level of bone resorption.

Normal range for men: 8.1–24.8 nmol bone collagen equivalent (BCE); *normal range for women:* 7.7–19.3 nmol BCE. The measurement of specific degradation products of the bone matrix (for example, metabolic markers of bone resorption and formation) provides analytical information concerning bone turnover.[61] Because of diurnal variation in the values for biochemical bone markers, early-morning sample collection is recommended for plasma/serum NTX, as well as for all other circulating bone markers. Increased osteoclast activity occurs soon after SCI and causes heightened bone resorption.[24,62,63] The level of bone resorption may be determined by measuring biochemical markers of the bone matrix in the circulation. NTX is the N terminal of the telopeptide of type 1 collagen, which is released during collagen degradation and has been used as a biochemical marker of bone resorption.

Spot urine N-telopeptide (NTX) concentration. This variable documents the level of bone resorption.

Normal range in adults: Men: 13–78 nmol BCE/mmol creatinine; women: 14–74 nmol BCE/mmol creatinine. This test should be performed early in the morning on a urine second void collection. The level of bone resorption may be measured by determining the urinary excretion of NTX.

Plasma/serum C-terminal telopeptide (CTX) concentration. This variable documents the level of bone resorption.

Normal range in adults: Men: 18–29 years = 90–1200 ng l^{-1}; 30–49 years = 70–800 ng l^{-1}; 50–68 years = 90–350 ng l^{-1}; >68 years = not established; women: 18–29 years = 60–650 ng l^{-1}; 30–49 years = 40–460 ng l^{-1}; 50–68 years = not established; >68 years = not established. CTX is the C terminal of the telopeptide of type 1 collagen, which is released during collagen degradation, and has been used as a biochemical marker of bone resorption. Because of diurnal variation in the values for biochemical bone markers, early-morning sample collection is recommended for plasma/serum CTX.

Plasma/serum osteocalcin concentration. This variable documents the level of bone formation.

Normal range in adults: 1.7–25 μg l^{-1}. Increased osteoblast activity may occur immediately after SCI, and it reflects increased bone turnover. The level of bone formation may be determined by measuring biochemical markers of the bone matrix in the circulation. Osteocalcin is a small noncollagenous protein that is synthesized by osteoblasts. Because of diurnal variation in the values for biochemical bone markers, early-morning sample collection is recommended for plasma/serum osteocalcin.

Plasma/serum procollagen type 1 N-terminal extension peptide (P1NP). This variable documents the level of bone formation.

Normal range in adults: Men: 30–110 μg l^{-1}; women: 20–106 μg l^{-1}. P1NP is derived from procollagen, which is cleaved to form type 1 collagen from the N-terminal propeptide. Similarly, early-morning sample collection is recommended for plasma/serum P1NP.

Dual-energy X-ray absorptiometry for bone mineral density. This variable documents bone mineral density (BMD) at skeletal sites of interest, including the distal femur, proximal tibia, total hip, femoral neck and radius (at one-third site).

In men and women aged 50 years or older, a *T*-score at or below −2.5 s.d. permits the diagnosis of osteoporosis. For determination of bone loss in men younger than 50 years of age and in premenopausal women, the *Z*-score should be used; a *Z*-score $\leqslant -2$ is defined as below the expected range for age (note: the diagnosis of osteoporosis cannot be made using the *Z*-score). For consistency, the recommendation is to use the NHANES III database (http://www.cdc.gov/nchs/nhanes/nh3data.htm#17a) (for consistency of end points, without using the proprietary databases of each manufacturer) for each patient, who would then have their scores matched to this reference database by age, gender and ethnicity. *T*-scores and *Z*-scores are not available for the distal femur and proximal tibia; as such, absolute scores for BMD of these regions of interest (ROI) should be obtained. If serial scans are to be acquired in order to follow potential bone loss, it would be important to standardize scans by their boney dimensions. At this time, only one company (GE Lunar) has FDA-approved software specifically to acquire the knee in the adult, but other companies have adapted other software packages for this purpose as well. If the ROI are meticulously obtained with appropriate software, then the results should be comparable, regardless of the software used to obtain the ROI. The International Society for Clinical Densitometry (ISCD) provides extensive, technical and clinical guidance on DXA acquisition, processing and reporting; despite the technical differences and challenges that are well appreciated to exist between able-bodied persons and those with SCI, this information may be of assistance in the acquisition of DXA images on patients with SCI (see: www.iscd.org).

Immobilization results in bone loss, which is dependent on the degree of inactivity and its duration.[21,64] Persons with more complete motor SCI who have the greatest neurological impairments and the most extreme degrees of physical immobilization would be expected to have the most rapid and marked bone loss, which appears to be progressive with the duration of injury.[7,20] The long-bone strength, and hence the risk of fractures, is related to bone mass and bone quality/microarchitecture.[65,66]

Thyroid function

Thyroid gland size. The size of the thyroid gland permits a clinical evaluation of its functional integrity. An enlarged thyroid gland, with a weight >20 g estimated by palpation and a volume >17 cm^3 by sonogram measurement,[67] may be the result of a functional disorder (either hyperthyroidism or hypothyroidism).

Plasma/serum TSH. This variable permits an evaluation of thyroid status.

Normal range: 0.5–5 mU l^{-1}. TSH measurement permits a biochemical evaluation of function of the thyroid gland.[68] An elevated TSH value would be consistent with hypothyroidism, whereas a suppressed value would suggest hyperthyroidism. TSH should be performed if there is clinical evidence of either hyperactivity (heat intolerance, excess sweating, unexplained weight loss, tachycardia and so on) or hypoactivity (cold intolerance, dry skin, unexplained weight gain, bradycardia and so on) of the thyroid gland.

Plasma/serum triiodothyronine (T_3). This variable permits an evaluation of thyroid status.

Normal range: 1.1–2.9 nmol l^{-1}. Triiodothyronine (T_3) or thyroxin (T_4) are hormones released by the thyroid gland, and their measurement permits a biochemical evaluation of the function of this gland.[68]

The plasma/serum T_3 determination should be performed if there is clinical evidence of a thyroid disorder. An elevated T_3 value would be consistent with hyperthyroidism, whereas a low value would suggest hypothyroidism.

Serum thyroxine (T_4). This variable similarly permits an evaluation of thyroid status.

Normal range: 64–154 nmol l^{-1}. The plasma/serum T_4 determination should be performed if there is clinical evidence of a thyroid disorder.[68] As for T_3, an elevated serum T_4 value would suggest hyperthyroidism, whereas a low value would suggest hypothyroidism.

Serum T_3 resin uptake (T_3RU). This variable permits an estimation of the serum thyroid hormone binding capacity and thereby permits an indirect evaluation of the functional status of the thyroid gland.

Normal range: 0.25–0.35. The T_3RU is a traditional means to indirectly estimate the free T_3 hormone concentration. In a competitive binding manner, radiolabeled thyroid hormone competes with endogenous, or unlabeled, thyroid hormone, to bind to a solid-phase matrix coated with T_3 antibody; the binding to the matrix is determined by the unoccupied serum T_3 binding sites (that is, number of thyroid globulin-binding sites) and the unlabeled, or endogenous, T_3. Thus, a high T_3RU value would occur if there is decreased serum thyroid binding globulin-binding sites and/or hyperthyroidism, whereas a low T_3RU value would occur if there is increased serum thyroid binding globulin-binding sites and/or hypothyroidism.

Serum free T_4. This variable permits a direct evaluation of the bioactive form of thyroid hormone and status of thyroid function.

Normal range: 9–16 pmol l^{-1}. Measurement of the serum FT_4 level determines the biologically active circulating T_4 hormone concentration. An elevated serum FT_4 value would be consistent with hyperthyroidism, whereas a low value would suggest hypothyroidism. If there is suspicion of pituitary and/or hypothalamic dysfunction (for example, central or secondary thyroid disorders), the FT_4 level should be obtained in addition to the serum/plasma TSH value to assess thyroid status.[68] In mild (or subclinical) hypothyroidism, the plasma/serum TSH level is, by definition, slightly elevated, whereas the FT_4 level is within the normal range.[68]

Thyroid antibodies. This variable permits determination of an autoimmune thyroid condition. If one or more anti-thyroid antibodies are determined to be present (that is, anti-thyroglobulin, anti-thyroid peroxidase and/or anti-TSH receptor), the presence of such antibodies will be recorded. The determination of thyroid antibodies should be performed if there is clinical evidence of a thyroid disorder that is not explained by other etiologies. Stress has been described to precipitate autoimmune thyroid disease in predisposed individuals.[36] In the general population, autoimmune thyroid disease is highly prevalent, with women disproportionally affected. As many as 50% of people in the community have microscopic nodules, 3.5% have occult papillary carcinoma, 15% have palpable goiters, 10% demonstrate an abnormal thyroid-stimulating hormone level and 5% of women have overt hypothyroidism or hyperthyroidism.[69] In the general population, thyroid antibodies are usually present and detectable in the presence of autoimmune disease, and there is no reason to assume otherwise in those with SCI.

Thyroid disease. This variable documents the presence of known thyroid disease. Pituitary–hypothalamic insult at the time of acute SCI, or in the immediate aftermath, should be considered. At the time of acute injury, in the absence of thyroid disease, thyroid function tests may be abnormal because of the stress of the event, intercurrent illness and/or dietary restriction.[6,70] However, as described above, stress has been described to precipitate thyroid disease in predisposed individuals,[36] and in the general population autoimmune thyroid disease is highly prevalent, with women disproportionally affected.

Thyroid disease: diagnostic classification. This variable identifies the specific diagnosis of thyroid disease: Graves' disease, Hashimoto's disease, diffuse toxic goiter, diffuse nontoxic goiter, nontoxic multinodular goiter, toxic multinodular goiter, acute thyroiditis, subacute thyroiditis, thyroid cancer, hyperfunctioning thyroid nodule and hypofunctioning thyroid nodule.

Adrenal function

Morning serum cortisol level. This variable documents adrenal function.

Normal range: 140–690 nmol l^{-1}. During periods of stress, a 'normal' serum cortisol level would be inappropriately low and suggest a deficiency state. Several of the symptoms of adrenal insufficiency may be found in persons with SCI, including weakness, gastrointestinal disorders, hypotension and syncope. As such, a high index of suspicion for the diagnosis should be entertained. Pre-existing adrenal insufficiency can be a life-threatening event in the setting of catastrophic illness. Although uncommon, abdominal injury/surgery may predispose to hemorrhage and necrosis of the adrenal glands, and/or central nervous system injury, especially with more severe injury, and may result in hypothalamic stalk and/or pituitary compromise.[16,71] Because of the catastrophic event of acute injury and the ever present potential for associated stressful events in the acute and subacute periods after injury, including hemorrhage, major organ damage, emergent and/or elective surgery, sepsis, coagulopathy, hypotensive and/or hypertensive crises, it is imperative to consider adrenal insufficiency at the time of presentation after acute SCI and until full medical stabilization.[19] Although less commonly prescribed than in the past, the administration of high-dose methylprednisolone in an effort to reduce acute neurological injury after traumatic SCI may be associated with adrenal suppression, which may present as intractable hypotension, related to, or independent of, an inter-current catastrophic event.[18] Even in the absence of antecedent glucocorticoid administration, persons with acute SCI may have adrenal insufficiency.[11] In those with chronic SCI, adrenal circadian rhythm and function has been shown to be generally normal,[72] but stimulation tests to determine adrenal reserve have shown abnormalities in functional capacity.[14]

24-h Urinary cortisol level. This variable documents adrenal function.

Normal range: 55–276 nmol/24 h. During periods of stress, a 'normal' 24-h urine cortisol excretion would be inappropriately low and suggest a deficiency state.

Gonadal function

Testicular size (men only). This variable documents anatomical abnormality of the testes.

Normal adult size testes: 3.5–5.5 cm in length. Gonadal size should be determined by an ordinary ruler, an orchidometer or by ultrasonography.[73] Examination of the testes is an essential part of the evaluation of testicular function. Because age does not influence testicular size *per se*, documenting small testes is a significant finding, regardless of the individual's age. Postpubertal damage to the testes may result in small, soft testes. Thus, the absence of small testes would

suggest the absence of significant damage to the seminiferous tubules (that is, end-organ injury).

Plasma/serum testosterone concentration (men only). This variable documents testicular function.

Normal range for men: 10–35 nmol l^{-1}. Because the serum testosterone concentration has a diurnal variation and falls throughout the day, it is recommended that levels be performed early in the morning.[74] Testosterone deficiency in the general population has been shown to occur in about 30% of men aged 40–79 years, with its prevalence increasing with more advanced age.[75,76] In persons with SCI, the prevalence of testosterone deficiency is significantly greater.[3] Clinical symptoms of testosterone deficiency include fatigue, decreased libido, erectile dysfunction and negative mood.[77,78] Testosterone has beneficial effects on body composition, specifically to maintain muscle mass and strength, as well as to reduce adiposity.[78,79] The question of testosterone replacement therapy in men shown to be deficient may be considered.[80] More recently, interest has focused on the metabolic abnormalities that may be increasingly prevalent with testosterone deficiency, including type 2 diabetes mellitus, hypertension and coronary artery disease.[81,82]

Serum sex hormone-binding globulin (men only). This variable permits the determination of free sex steroids.

Normal range: 9.5–65 nmol l^{-1} (for men). Hormones that are insoluble in water require carrier mechanisms, transport proteins. The transport proteins function as reservoirs, with the hormones being in dynamic equilibrium of being bound or free, with a small fraction of free hormone in the circulation. Only the free hormone enters cells and has biological activity. Sex hormones (for example, testosterone and estrogen) are weakly bound to albumin (~60%) and more tightly bound to a circulating binding protein, sex hormone-binding globulin (SHBG) (~40%). The free and non-SHBG hormone concentrations, often referred to as 'bioactive' testosterone concentration, can be calculated from the total testosterone concentration, serum albumin concentration and SHBG value.[83]

Serum albumin (men only). This variable permits the determination of serum albumin.

Normal range: 540–740 μmol l^{-1}. Please refer to the comments above on serum SHBG. Albumin weakly binds hormones that are transported in the circulation.

Serum bioactive testosterone (men only). This variable permits the determination of bioactive testosterone.

Normal range: 2600–17 600 pmol l^{-1} (for men). Serum bioactive testosterone represents the fraction of circulating total testosterone that is either free or loosely bound to albumin (~60% of total testosterone concentration). Because the serum testosterone concentration has a diurnal variation and falls throughout the day, it is recommended that levels be drawn early in the morning.[74] The bioactive testosterone is hypothesized to be the more active components of total testosterone. The free and 'bioactive' hormone concentrations can be calculated as described from the total serum sex steroid concentration, serum albumin concentration and SHBG value.[83]

Serum free testosterone (men only). This variable permits the determination of free testosterone.

Normal range: 113–750 pmol l^{-1} (for men). Serum free testosterone represents the fraction of circulating total testosterone that is not bound to SHBG or albumin (~2% of total testosterone concentration). As stated above, it is recommended to be drawn early in the morning.[74] The free testosterone is hypothesized to be the most active component of total testosterone. For calculation of free testosterone, refer to the above text along with the reference provided.[83]

Plasma/serum estradiol concentration (women only). This variable documents ovarian hormonal function.

Normal range women: basal, 70–220 pmol l^{-1}; ovulatory surge, >740 pmol l^{-1}; postmenopausal, 40 pmol l^{-1}. Estradiol concentrations reflect the integrity of ovarian sex hormone production, which also reflects the function of the hypothalamic–pituitary axis to release gonadotropins in an appropriate manner.

Pituitary function

Plasma prolactin concentration. This variable documents hypothalamic–pituitary integrity and dopaminergic tone.

Normal-range men and nonpregnant women: 39–102 mmol l^{-1}. Plasma prolactin concentrations increase in the presence of reduced dopaminergic tone. It has been suggested that persons with chronic SCI have a dysfunction of central dopaminergic tone that may affect pituitary prolactin release, with a subset of persons with chronic SCI having elevated basal levels of plasma prolactin and a larger subset having a heightened plasma prolactin response after provocative stimulation.[8]

Plasma luteinizing hormone concentration. This variable documents pituitary gonadotropic function.

Normal range for men: 1.3–13 IU l^{-1}. The effects of SCI on sexual organs and function generally have different clinical courses in men and women. Pituitary–hypothalamic insult at the time of acute SCI, or in the immediate aftermath, should be considered. In men with chronic SCI, reports have appeared to suggest that testosterone levels are depressed, with abnormalities of the pituitary–hypothalamic regulation of the gonads.[8,84]

Normal range for women: basal, 0.8–26; ovulatory surge, 25–57 (time of menstrual cycle to be determined by clinical assessment using subjective information); postmenopausal, 40–104 IU l^{-1}.

Although menses may be temporarily interrupted at the time of acute injury, the menstrual cycle usually returns thereafter, with full capacity to conceive.[13]

Plasma follicular-stimulating hormone concentration. This variable, similarly, documents pituitary gonadotropic function.

Normal range for men: 0.9–15 IU l^{-1}. *Normal range for women:* basal, 1.4–9.6; ovulatory surge, 2.3–21; postmenopausal, 34–98 IU l^{-1}.

Plasma insulin-like growth factor-1. This variable will permit evaluation of integrated plasma growth hormone concentrations.

Normal range for men: 0.34–2.2 kU l^{-1}. *Normal range for women:* 0.45–1.9 kU l^{-1}. Pituitary–hypothalamic dysfunction may occur in persons with SCI at the time of acute SCI or may develop years afterward. The response of growth hormone to provocative stimulation has been shown to be blunted in persons with SCI. Plasma insulin-like growth factor, in the absence of liver disease, provides an estimate of integrated daily growth hormone release.[4]

Plasma copeptin. This variable reflects the secretion of vasopressin by the posterior pituitary.

Normal range: 1.7–11.25 pmol l^{-1}. Central diabetes insipidus results from the inability to secrete vasopressin to appropriately concentrate the urine. If there is clinical suspicion for diabetes insipidus, which would include a hyperosmolar state (for example, hypernatremia) in

association with relatively diluted urine, a plasma copeptin level should be considered. Vasopressin secretion is pulsatile and its residence time in the circulation is low. As such, the measurement of copeptin, the C-terminal portion of pre-provasopressin (that is, a peptide secreted in equimolar amounts to vasopressin) affords a practical alternative to measurement of vasopressin.[85,86] If during fluid restriction the serum copeptin concentration does not increase, and/or the serum sodium concentration is elevated in the presence of dilute (hypo-osmolar) urine, a dysfunction of vasopressin release from the posterior pituitary may be present. A fluid deprivation test with desmopressin should be considered.

Fluid deprivation test with desmopressin (DDAVP). This variable permits evaluation for diabetes insipidus.

Normal response: >50% in urine osmolarity (positive test). Posterior pituitary dysfunction may occur in persons with SCI at the time of acute SCI, or may develop years afterward.[15,17,87] Head trauma not infrequently occurs with SCI, with as high as 60% of those with traumatic SCI also sustaining a TBI,[88] and 2% of cases of head trauma cases have been reported to be associated with diabetes insipidus.[89] If there is a central deficiency of vasopressin (also known as antidiuretic hormone), then there will be difficulty in concentrating the urine (<300 mosmol l^{-1}) and an increase in urine volume (>50 ml kg^{-1}) may occur. If there is clinical suspicion for diabetes insipidus, which would include a hyperosmolar state (for example, hypernatremia) in association with urine, which is relatively dilute, a fluid deprivation test should be considered. After ad libitum fluid intake, fluid intake is restricted (usually in the morning) until urine concentration increases to >300 mosmol l^{-1} or increases to a specific gravity >1.010. However, before the body weight decreases by 5% during fluid restriction, and if the urine does not concentrate and the plasma osmolarity and/or serum sodium concentration exceed the upper limit of normal, then intravenous or subcutaneous desmopressin (DDAVP, 0.03 μg kg^{-1}) should be administered with the urine osmolarity measured 1–2 h later. If the urine concentrates sufficiently after DDAVP administration, then central diabetes insipidus is diagnosed; if the urine does not concentrate after DDAVP, renal resistance to DDAVP is to be considered.

Sympathetic nervous system function

Plasma norepinephrine concentration. This variable documents the integrity of the sympathetic nervous system.

Normal range: supine = 0.74–1.41 nmol l^{-1}; seated/standing = 1.68–2.44 nmol l^{-1}. Impairment of autonomic (for example, sympathetic nervous system) integrity will compromise the ability to maintain blood pressure with upright posture because of the absence of a vasopressor response.[37,90] Norepinephrine (NE) is a neurotransmitter released by postsynaptic sympathetic neurons, which binds to the vascular walls, causing peripheral vasoconstriction, thereby opposing hemodynamic fluid shifts to the dependent circulation during upright positioning. Inadequate postsynaptic NE release results in hemodynamic instability and orthostatic hypotension.[91,92] Levels of plasma NE are low in persons with cervical SCI in the supine resting position (0.40 nmol l^{-1})[10,38,93] and upright positions (0.75 nmol l^{-1}).[9] In persons with a higher cord lesion who appear to have difficulty in maintaining blood pressure with upright positioning, partial or total ablation of the sympathetic response should be considered, which may be reflected by resting supine levels below 0.56 nmol l^{-1} and an attenuated plasma NE response to head-up tilt.[9,38]

Renin–aldosterone axis function

Plasma renin activity. This variable documents the integrity of one component of the renal response to hypotension.

Normal range: supine = 0.3–3 ng ml^{-1} h^{-1}; seated/standing = 0.7–5 ng ml^{-1} h^{-1}. Plasma renin activity is reported to be elevated in response to head-up tilt in persons with cervical SCI.[9,10] Normal salt and water metabolism is essential for maintenance of cardiovascular homeostasis. With a fall in blood pressure, the renin–aldosterone system is activated.[9,10,94] In the presence of renal insufficiency, a deficient plasma renin response will result in impaired renal retention of salt and water because of the inability to appropriately stimulate aldosterone release from the adrenal cortex.

Serum aldosterone. This variable documents the integrity of one component of the adrenal cortical response to hypotension.

Normal range (normal diet): supine $\leqslant 240$ pmol l^{-1}; seated/standing = 140–560 pmol l^{-1}. Serum aldosterone concentrations are within the normal range in persons with cervical SCI in the supine position (228 pmol l^{-1}), but heightened serum aldosterone responses to head-up tilt have been reported (700 pmol l^{-1}).[9,10] Appropriate regulation of salt and water metabolism to upright posture by activation of the renin–aldosterone system is essential for maintenance of cardiovascular homeostasis.[9,94] A deficient serum aldosterone response to upright posture will result in impaired hemodynamic regulation because of the inability to appropriately retain salt and water by the kidney.

DISCUSSION

The data collected in the ISCIEMEDS will usually be available in conjunction with the data in the International SCI Core Data Set, which, among other items, include information on date of birth and injury, gender, the cause of SCI and neurological status.[40] In addition, it will similarly be viewed together with the International SCI Endocrine and Metabolic Basic Data Set. This Basic Data Set includes items covering the most clinically relevant information regarding possible endocrine and metabolic dysfunction in persons with SCI, whereas the ISCIEMEDS will not be intended for widespread clinical use, but primarily intended for clinical research purposes. Still, when considering specific areas with regard to the endocrine and metabolic challenges for persons with SCI, the ISCIEMEDS will be able to inform and guide the clinician concerning the endocrine and metabolism information, which could be appropriate to obtain, as described in this data set.

To facilitate the use of the International SCI Data Sets, this ISCIEMEDS and its data collection (the form is included in the Appendix) have been developed similarly to that of previous International SCI Basic Data Sets. To validate and translate this data set into use, additional effort and study will be needed. The authors invite all those who are interested to participate in this open and ongoing process.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

INTERNATIONAL SPINAL CORD INJURY ENDOCRINOLOGY AND METABOLISM EXTENDED DATA SET — DATA FORM (Version 1.0)

Carbohydrate Metabolism:
Plasma glucose:
Fasting _____ mmol/L; Date YYYYMMDD; □ Unknown
2 hours _____ mmol/L; Date YYYYMMDD; □ Unknown
OGTT diagnostic classification: □ normal; □ Impaired Glucose Tolerance; □ Diabetes Mellitus

Plasma insulin: Fasting _____ pmol/L; Date YYYYMMDD; □ Unknown
2 hours _____ pmol/L; Date YYYYMMDD; □ Unknown

Hemoglobin A1c: _____%; Date YYYYMMDD; □ Unknown

Calcium & Bone Metabolism:
Plasma/Serum calcium _____mmol/L; Date YYYYMMDD; □ Unknown
Plasma ionized calcium _____mmol/L Date YYYYMMDD; □ Unknown
Urine calcium _____ mmol/24 hours; Date YYYYMMDD; □ Unknown
Urine calcium/creatinine _____ mmol/mg; Date YYYYMMDD; □ Unknown
Serum 25-OH D: ___ nmol/L; Date YYYYMMDD; □ Unknown
Plasma parathyroid hormone (PTH) level: ___ ng/L; Date YYYYMMDD; □ Unknown

Plasma/Serum N-telopeptide _____ nmol BCE; Date YYYYMMDD; □ Unknown
Urine N-telopeptide _____ nmol BCE/mmol creat; Date YYYYMMDD; □ Unknown
Plasma/Serum C-telopeptide _____ ng/L; Date YYYYMMDD; □ Unknown
Plasma/Serum osteocalcin _____ µg/L; Date YYYYMMDD; □ Unknown
Plasma/Serum P1NP_____ µg/L; Date YYYYMMDD; □ Unknown

Dual energy x-ray absorptiometry: Date YYYYMMDD; □ Unknown
If osteoporosis (-2.5 or less SD) is present for persons ≥50 years old, place an "X" in the space provided for each skeletal site of interest:
Total Hip _____ Femoral neck _____ Radius _____
Bone mineral density (BMD) for each the skeletal sites of interest:
Total Hip _____ (g/cm^2)
Femoral neck _____ (g/cm^2)
Distal femur _____ (g/cm^2)
Proximal tibia _____(g/cm^2)
Radius _____ _____(g/cm^2)

If Z-values are below the expected range for age for persons <50 years old, place an "X" in the space provided:
Hip _____ (-2.0 or less SD) Radius _____ (-2.0 or less SD)

Thyroid Function:
Goiter: □absent □ present; Date YYYYMMDD; □ Unknown
Plasma/Serum thyroid stimulating hormone (TSH) ____ mU/L;
Date YYYYMMDD; □ Unknown
Plasma/Serum triiodothyronine (T3) _____nmol/L Date YYYYMMDD; □ Unknown
Serum thyroxine (T4) _____nmol/L Date YYYYMMDD; □ Unknown
Serum T_3 resin uptake (T_3RU) _____ Date YYYYMMDD; □ Unknown
Plasma/Serum free thyroxine (FT_4) _____ Date YYYYMMDD; □ Unknown

Thyroid antibodies: □ absent □ present; Date YYYYMMDD; □ Unknown
Thyroid disease: □ absent □ present; Date disease diagnosed YYYYMMDD; □ Unknown
Thyroid diagnosis: □ Hashimoto's disease; □ Diffuse toxic goiter; □ Diffuse nontoxic goiter; □ Nontoxic multinodular goiter; □ Toxic multinodular goiter; □ Acute thyroiditis; □ Subacute thyroiditis; □ Thyroid cancer; □ Hyperfunctioning thyroid nodule; □ Hypofunctioning thyroid nodule; □ Other

Adrenal Function:
06-08 (a.m.) fasting serum cortisol ____ nmol/L; Date YYYYMMDD; □ Unknown
24-hour urine cortisol ____ nmol/24 hours; Date YYYYMMDD; □ Unknown

Gonadal Function:
Men:
Testis □ normal size □ small; Date YYYYMMDD; □ Unknown
Plasma/Serum testosterone _____ nmol/L; Date YYYYMMDD; □ Unknown
Serum sex hormone binding globulin _____ nmol/L Date YYYYMMDD; □ Unknown
Serum albumin _____ µmol/L Date YYYYMMDD; □ Unknown
Serum bioactive testosterone _____ pmol/L Date YYYYMMDD; □ Unknown
Serum free testosterone _____ pmol/L Date YYYYMMDD; □ Unknown
Women:
Plasma/Serum estradiol _____ pmol/L; Date YYYYMMDD; □ Unknown

Pituitary Function:
Anterior Pituitary:
Plasma Prolactin _____ mmol/L; Date YYYYMMDD; □ Unknown
Men:
Plasma luteinizing hormone (LH) _____ IU/L; Date YYYYMMDD; □ Unknown
Plasma follicular stimulating hormone (FSH) _____ IU/L; Date YYYYMMDD; □ Unknown
Plasma insulin-like growth factor-1 (IGF-1) (baseline) _____ kU/L;
Date YYYYMMDD; □ Unknown
Women:
Plasma LH _____ IU/L; Date YYYYMMDD; □ Unknown
Plasma FSH _____ IU/L; Date YYYYMMDD; □ Unknown
Identify the time of menstrual cycle (basal, ovulatory surge, postmenopausal) _____
Plasma IGF-1 (baseline) _____ kU/L; Date YYYYMMDD; □ Unknown
Posterior Pituitary:
Plasma copeptin _____ pmol/L; Date YYYYMMDD; □ Unknown
Fluid deprivation test with DDAVP □ positive □ negative Date YYYYMMDD; □ Unknown

Sympathetic Nervous System Function:
Plasma norepinephrine supine _____ nmol/L Date YYYYMMDD; □ Unknown
Plasma norepinephrine seated/standing _____ nmol/L Date YYYYMMDD; □ Unknown

Renin-Aldosterone Axis Function:
Plasma renin supine _____ ng/mL/h Date YYYYMMDD; □ Unknown
Plasma renin seated/standing _____ ng/mL/h Date YYYYMMDD; □ Unknown
Serum aldosterone supine _____ pmol/L Date YYYYMMDD; □ Unknown
Serum aldosterone seated/standing _____ pmol/L Date YYYYMMDD; □ Unknown

Conversion Factor (CF) × Conventional (C) = System of International Units (SI)

Glucose	0.05551 × mg/dL = mmol/L
Insulin	7.175 × µU/mL = pmol/L
Total Calcium (plasma)	0.2595 × mg/dL = mmol/L

25-Hydroxycholecalciferol (25-OH-D)	2.496 × ng/dL = nmol/L
Thyroxine (T_4)	12.87 × µg/dL = nmol/L
Triiodothyronine (T_3)	0.0154 × ng/dL = nmol/L
Free Thyroxine (FT_4)	12.85 × ng/dL = pmol/L
Cortisol	27.59 × µg/dL = nmol/L
Testosterone	4.467 × ng/mL = nmol/L
Estradiol	3.671 x pg/ml = pmol/L
Creatinine	88.4 x mg/dL = µmol/L
Other conversions:	pg/mL = ng/L
	ng/mL = µg /L
	µU/mL = mU/L
	mU/mL = U/L
	U/mL = kU/L